

Supplemental Appendix 2

This supplement contains the following:

- Final approved TRILOGY ACS study protocol (with change summary)
- The TRILOGY ACS statistical analysis plan
- The TRILOGY ACS electronic case report form (eCRF)
- TRILOGY ACS Neoplasm Clinical Endpoint Committee Charter
- TRILOGY ACS Neoplasm Study Statistical Analysis Plan

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Protocol H7T-MC-TABY(b) A Comparison of Prasugrel and Clopidogrel in Acute Coronary Syndrome (ACS) Subjects with Unstable Angina/Non-ST-Elevation Myocardial Infarction (UA/NSTEMI) Who are Medically Managed – The TRILOGY ACS Study

Prasugrel hydrochloride (LY640315)

Study H7T-MC-TABY(b) (TRILOGY ACS) is a Phase 3, multicenter, randomized, parallel-group, double-blind, double-dummy, active-controlled study in subjects who have experienced recent (within 10 days) unstable angina/non-ST-elevation myocardial infarction (UA/NSTEMI) acute coronary syndromes (ACS) and who are to be medically managed.

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Protocol Approved by Lilly: 28 August 2007
Amendment (a) Approved by Lilly: 06 February 2008
Amendment (b) Approved by Lilly: 05 May 2009

A Comparison of Prasugrel and Clopidogrel in Acute Coronary Syndrome (ACS) Subjects with Unstable Angina/Non-ST-Elevation Myocardial Infarction (UA/NSTEMI) Who are Medically Managed - The TRILOGY ACS Study

Table of Contents

Section	Page
1. Introduction.....	12
1.1. Background Information on Prasugrel	12
1.2. Rationale for the Current Study	13
1.2.1. Medical Management as a Strategy in UA/NSTEMI ACS	14
1.2.2. Dual Antiplatelet Therapy in the Medical Treatment of ACS	15
1.2.3. TRILOGY ACS: Evaluating Unanswered Questions in the Medically Managed UA/NSTEMI ACS Population	16
1.2.4. Conclusions	17
2. Objectives	19
2.1. Primary Objective	19
2.2. Secondary Objectives	19
2.2.1. Efficacy Objectives	19
2.2.2. Safety Objectives	19
2.3. Substudy Objectives	20
2.3.1. Platelet Function Substudy	20
2.3.1.1. Pharmacodynamic Objectives	20
2.3.1.2. Genomic Objectives.....	21
2.3.1.3. Other Objectives	21
2.3.2. Health Outcome Substudy Objectives.....	21
2.4. Other Objectives.....	22
3. Investigational Plan	23
3.1. Summary of Study Design.....	23
3.1.1. Study Operations and Medical Oversight.....	29
3.2. Discussion of Design and Control.....	29
4. Study Population	32

4.1.	Inclusion Criteria.....	32
4.1.1.	Disease Diagnostic Criteria	33
4.1.1.1	Definition of UA/NSTEMI	33
4.1.1.2	Decision for Medical Management	33
4.1.2.	Standard of Care for Commercial Clopidogrel Use in UA/NSTEMI Subjects.....	33
4.2.	Exclusion Criteria.....	34
4.2.1.	Rationale for Exclusion of Certain Study Candidates.....	37
4.2.2.	Enrollment (Randomization) Criteria.....	37
4.3.	Discontinuations.....	37
4.3.1.	Subjects Inadvertently Enrolled	37
4.3.2.	Temporary Discontinuation of Study Drug	38
4.3.2.1.	Temporary Discontinuation of Study Drug due to a Bleeding Event.....	38
4.3.2.2.	Study Drug Management for Percutaneous Coronary Intervention.....	39
4.3.2.3.	Temporary Discontinuation of Study Drug due to Coronary Artery Bypass Graft Surgery	39
4.3.2.4.	Temporary Discontinuation of Study Drug due to Other Medical or Surgical Procedures.....	39
4.3.3.	Permanent Discontinuation of Study Drug.....	40
4.3.4.	Discontinuation from the Study	41
4.3.5.	Subjects Lost to Follow-Up	41
4.3.6.	Discontinuation of Study Sites.....	41
4.3.7.	Discontinuation of the Study	42
5.	Treatment.....	43
5.1.	Treatments Administered.....	43
5.2.	Materials and Supplies.....	44
5.3.	Method of Assignment to Treatment.....	44
5.4.	Rationale for Selection of Doses in the Study	44
5.4.1.	Background	44
5.4.2.	Rationale for Selection of the Loading Dose in TRILOGY ACS	45
5.4.3.	Rationale for the Selection of the Maintenance Dose in TRILOGY ACS	45
5.5.	Timing of Doses	46
5.6.	Blinding	47
5.7.	Concomitant Therapy	47
5.8.	Treatment Compliance	49

6.	Efficacy Measures, Health Outcome Measures, and Safety Evaluations	50
6.1.	Efficacy Endpoints	50
6.1.1.	Primary Efficacy Measure	50
6.1.2.	Secondary Efficacy Endpoints	51
6.1.2.1.	Rehospitalization for recurrent UA	52
6.1.2.2.	Stent thrombosis	52
6.1.2.3.	Platelet Function Measures	53
6.1.2.3.1.	Other Biomarkers.....	54
6.1.2.3.2.	Stored Samples	54
6.1.3.	Sample Banking	54
6.2.	Health Outcome Measures.....	55
6.3.	Safety Evaluations.....	55
6.3.1.	Safety Endpoints	56
6.3.1.1.	Bleeding events	56
6.3.2.	Adverse Events	57
6.3.2.1.	Serious Adverse Events	58
6.3.2.2.	Non-benign Neoplasm	59
6.3.3.	Other Safety	59
6.3.4.	Safety Monitoring	60
6.3.5.	Complaint Handling	60
6.4.	Appropriateness of Measurements	61
7.	Data Quality Assurance	62
7.1.	Data Entry and Computerized Systems	62
8.	Sample Size and Statistical Methods	63
8.1.	Determination of Sample Size	63
8.2.	Statistical and Analytical Plans.....	64
8.2.1.	General Considerations	64
8.2.2.	Subject Disposition	65
8.2.3.	Subject Characteristics	65
8.2.4.	Concomitant Therapy	65
8.2.5.	Treatment Compliance	65
8.2.6.	Primary Outcome and Methodology	66
8.2.7.	Efficacy Analyses – Secondary Endpoints	66
8.2.8.	Health Outcome Analyses	68
8.2.9.	Safety Analyses	68
8.2.9.1.	Safety Endpoint Analyses	68
8.2.9.2.	Adverse Event and Laboratory Analyses.....	69

8.2.10.	Subgroup Analyses for Efficacy and Safety	69
8.2.11.	Interim Analyses	70
8.2.11.1.	Frequency and Objectives of Interim Reports.....	70
8.2.11.2.	Early Termination due to Excessive Life Threatening Bleeding or Deaths.....	70
9.	Informed Consent, Ethical Review, and Regulatory Considerations.....	72
9.1.	Informed Consent	72
9.2.	Ethical Review	72
9.3.	Regulatory Considerations.....	73
9.3.1.	Investigator Information	73
9.3.2.	Protocol Signatures	73
9.3.3.	Final Report Signature.....	73
10.	References.....	74

Table of Contents (concluded)

List of Protocol Attachments

Protocol Attachment TABY.1.

Study Schedule

Protocol Attachment TABY.2.

Clinical Laboratory Tests

Protocol Attachment TABY.3.

Health Outcomes Substudy

Protocol Attachment TABY.4.

New York Heart Association Congestive Heart Failure Classifications

Abbreviations and Definitions

ACC	American College of Cardiology
ACEI	angiotensin converting enzyme inhibitor
ACS	acute coronary syndromes
ADP	adenosine diphosphate
ALT/SGPT	Alanine aminotransferase/serum glutamic pyruvic transaminase
AHA	American Heart Association
ANOVA	analysis of variance
ARB	angiotensin receptor blocker
ARO	academic research organization
ASA	Aspirin
Assent	Agreement from a child or other individual who is not legally capable of providing consent, but who can understand the circumstances and risks involved in participating in a study (required by some Institutional Review Boards [IRBs]).
AST/SGOT	aspartate aminotransaminase/serum glutamic oxaloacetic transaminase
Audit	A systematic and independent examination of the study-related activities and documents to determine whether the evaluated study-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).
BASE	Internal standard in the Accumetrics VerifyNow® P2Y12 platelet aggregation assay
Blinding	A procedure in which one or more parties to the study are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to the subject(s), investigator(s), monitor(s), and in some cases, select sponsor personnel being unaware of the treatment assignment(s).
BNP	brain natriuretic peptide
BUN	blood urea nitrogen

CABG	coronary artery bypass graft
CAD	coronary artery disease
CEC	Clinical Endpoints Committee
CHF	congestive heart failure
CK-MB	creatinine kinase-MB fraction (primarily in cardiac muscle)
CLO	clopidogrel
Complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
Compliance	Adherence to all the study-related requirements, GCP requirements, and the applicable regulatory requirements.
COX2	cyclooxygenase-2
CRF	case report form (sometimes referred to as clinical report form). A printed or electronic form for recording study subjects' data during a clinical study, as required by the protocol.
CRO	contract research organization
CT	computed tomography
CV	cardiovascular
DAG	data analysis group
DCRI	Duke Clinical Research Institute
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
End of Study (Trial)	End of study (trial) is defined as the date of the last visit or last scheduled procedure at the last site shown in the Study Schedule for the last active subject in the study.
Enroll	See Study Entry Terms
Enter	See Study Entry Terms
ERB	Ethics Review Board
ESC	European Society of Cardiology
GCP	Good Clinical Practice

GUSTO	Global Use of Strategies to Open Occluded Coronary Arteries
H2	histamine 2 receptor
Hct	hematocrit
HDL	high density lipoprotein
Hgb	hemoglobin
HMG Co-A	3-hydroxy-3-methylglutaryl coenzyme A
hs-CRP	high-sensitivity C-reactive protein
ICH	intracranial hemorrhage
IND	Investigational New Drug
INR	International Normalized Ratio
Interim Analysis	Any analysis intended to compare treatment groups at any time prior to the formal completion of a study.
Investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
IPA	inhibition of platelet aggregation
IRB/ERB	Institutional Review Board/Ethical Review Board: a board or committee (institutional, regional, or national) composed of medical professional and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the subjects participating in a clinical study are protected.
ITT	intent-to-treat
IVRS	interactive voice response system
LD	loading dose (of study drug)
LDL	low density lipoprotein
Legal Representative	An individual, judicial, or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study.
LTA	light transmission aggregometry
MACE	major adverse cardiovascular events
MD	maintenance dose (of study drug)
MI	myocardial infarction

MM	medical management
MQA	(Lilly) Medical Quality Assurance
MRI	magnetic resonance imaging
NSAID	nonsteroidal anti-inflammatory drug
NSTEMI	non-ST-segment elevation myocardial infarction
NT-proBNP	N-terminal prohormone brain natriuretic peptide
NYHA	New York Heart Association
Patient	A subject with a defined disease.
PCI	percutaneous coronary intervention
PPI	proton-pump inhibitors
PRU	P2Y ₁₂ Reaction Unit
RBC	red blood cell
SOC	Study Operations Committee
SOP	Standard operating procedure
STEMI	ST-segment elevation myocardial infarction
Study Entry Terms	<p>Enroll</p> <p>The act of assigning a subject to a treatment. Subjects who are enrolled in the study are those who have been assigned to a treatment.</p> <p>Enter</p> <p>The act of obtaining informed consent for participation in a clinical study from subjects deemed eligible or potentially eligible to participate in the clinical study. Subjects entered into a study are those who sign the informed consent document directly or through their legally acceptable representatives.</p> <p>Screen</p> <p>The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.</p>
Study Operations Committee	The study operations committee is comprised of members from the Sponsor, CRO, and ARO.
Subject	An individual who is or becomes a participant in clinical research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.
SV	site visit
TC	telephone contact

TEAE	treatment-emergent adverse event
TIMI	Thrombolysis in Myocardial Infarction Study Group
TRAP	Thrombin Receptor Activating Peptide
TRILOGY-ACS	Another name for H7T-MC-TABY
UA	unstable angina
ULN	upper limit of normal
US	United States
VASP	vasodilator-associated stimulated phosphoprotein
WBC	white blood cell

A Comparison of Prasugrel and Clopidogrel in Acute Coronary Syndrome (ACS) Subjects with Unstable Angina/Non-ST-Elevation Myocardial Infarction (UA/NSTEMI) who are Medically Managed

1. Introduction

Prasugrel hydrochloride (CS-747, LY640315, hereafter referred to as prasugrel) is a new thienopyridine adenosine diphosphate (ADP) receptor antagonist. Prasugrel provides faster onset of action, higher levels of platelet inhibition, and less response variability compared with clopidogrel, the current standard of care for dual antiplatelet therapy in subjects with acute coronary syndromes (ACS), such as unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI). In the Phase 3 study TRITON-TIMI 38 (Wiviott et al. 2006; Wiviott et al. 2007[a]), prasugrel significantly reduced the rate of atherothrombotic events in subjects with ACS undergoing percutaneous coronary intervention (PCI). The present study, H7T-MC-TABY (hereafter referred to as “TRILOGY ACS”), will include subjects who have experienced recent (within 10 days) UA and NSTEMI and who will be managed without acute coronary revascularization; that is, who will be medically managed.

1.1. Background Information on Prasugrel

Prasugrel is an orally administered, rapidly absorbed, pro-drug requiring in vivo metabolism to form the active metabolite (R-138727) that irreversibly inhibits platelet activation and aggregation mediated by the P2Y₁₂ receptor (Niitsu et al. 2005). Prasugrel's distinct chemical structure permits efficient conversion, through rapid hydrolysis by carboxylesterases and then by multiple cytochrome P450 (CYP) enzymes, which is key to its high active metabolite exposure and high levels of platelet inhibition (Sugidachi et al. 2007; Wallentin et al. 2008; Payne et al. 2007).

In the clinical development of prasugrel, multiple studies have been conducted in healthy subjects, as well as in stable coronary artery disease (CAD) and ACS subjects, with exposure to various prasugrel loading doses (LD) and maintenance doses (MD). The majority of studies were placebo-controlled or active-comparator (clopidogrel) controlled and subjects were randomly assigned, in an open-label or blinded fashion, to treatment using either parallel or crossover designs. Across all studies as of 16 November 2008, approximately 9,174 subjects received at least 1 dose of prasugrel. The majority (73.5%) of exposure data are derived from 6741 subjects in TRITON-TIMI 38. Approximately 60% of these subjects were exposed for ≥365 days and approximately 40% were exposed for ≥450 days.

Phase 1 and 2 studies demonstrated that prasugrel, in single doses up to 80 mg and repeat doses up to 15 mg for approximately one month, had an acceptable overall safety profile. The prasugrel 15-mg MD, however, was associated with a trend toward greater bleeding and study drug discontinuation for bleeding TEAEs in the studies of stable CAD subjects (Jernberg et al. 2006) and subjects undergoing urgent or elective PCI (JUMBO – TIMI 26; Wiviott et al. 2005). Pharmacodynamic analyses showed superior platelet inhibition and less variability with the prasugrel 60/10-mg LD/MD regimen compared to either the approved 300/75-mg LD/MD clopidogrel dosing regimen (Jakubowski et al. 2007; Brandt et al. 2007; Jernberg et al. 2006; Payne et al. 2007) or the higher, non-approved 600/150-mg LD/MD clopidogrel dosing regimen (Payne et al. 2007; Wallentin et al. 2008; Wiviott et al. 2007[b]). Since prasugrel 60/10-mg LD/MD did not significantly increase the rate of TIMI Major and Minor bleeding compared to clopidogrel in JUMBO – TIMI 26, this regimen was selected for the TRITON-TIMI 38 study.

TRITON-TIMI 38, to date the largest clinical study comparing two thienopyridine antiplatelet agents, randomized 13,608 moderate-to-high-risk ACS subjects undergoing PCI to either prasugrel (a 60- mg LD followed by a 10-mg daily MD) or the approved clopidogrel regimen (a 300-mg LD followed by a 75-mg daily MD), both administered with low-dose aspirin, for 6 to 15 months. Prasugrel, as compared with clopidogrel treatment, was associated with a significant reduction in the occurrence of the composite primary efficacy endpoint of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke (9.9% versus 12.1%; hazard ratio 0.81; 95% confidence interval [CI], 0.73 to 0.90; $P < 0.001$). There were also significantly reduced rates of ischemic events in the prasugrel group: myocardial infarction (7.4% versus 9.7%; $p < 0.001$), urgent target-vessel revascularization (2.5% versus 3.7 %; $p < 0.001$) and stent thrombosis (1.1 % versus 2.4%; $p < 0.001$). Overall mortality did not differ significantly between treatment groups. Prasugrel increased the risk of non-CABG associated TIMI major bleeding (2.4 % versus 1.8%; $p = 0.03$), as well as life-threatening (1.4% versus 0.9%; $p = 0.01$) and fatal bleeding (0.4% versus 0.1%; $p = 0.002$). However, net clinical benefit was observed with prasugrel across the entire spectrum of subjects with ACS managed by PCI. While Study TAAL (TRITON-TIMI 38) was designed as a pivotal superiority study to directly compare CV outcomes in subjects treated with prasugrel and clopidogrel, it is also the first adequately powered clinical study to test the hypothesis that the higher and more consistent level of platelet inhibition previously demonstrated with prasugrel versus standard dose clopidogrel would result in reduced ischemic events in the setting of ACS managed by PCI.

1.2. Rationale for the Current Study

TRILOGY ACS will complement the TRITON-TIMI 38 Study by evaluating the relative efficacy and safety of prasugrel and clopidogrel in a distinctly different UA/ NSTEMI ACS population: the medically managed. Thus, TRILOGY ACS will serve as the first study of sufficient size to assess whether a dosing regimen that achieves greater inhibition of platelet function than the approved dosing for clopidogrel will improve

clinical outcomes for subjects who are not managed with acute coronary revascularization. As in TRITON-TIMI 38, TRILOGY ACS will study the use of prasugrel in UA/NSTEMI ACS populations only after the decision for acute management is clear. Specifically, the intent for both of these study designs is to avoid excessive bleeding risk with prasugrel by enrolling subjects only after determination, with reasonable certainty, that coronary artery bypass grafting (CABG) surgery will not be performed for the index ACS event.

1.2.1. Medical Management as a Strategy in UA/NSTEMI ACS

Options for the initial management of UA/NSTEMI ACS include pharmacotherapy alone or an early invasive strategy with PCI (with or without coronary stenting) or coronary artery bypass grafting (CABG) as guided by the results of coronary angiography. For subjects with intermediate to high-risk features, current ACC/AHA and ESC guidelines endorse an early invasive strategy with prompt coronary angiography and revascularization (Anderson et al. 2007; Bassand et al. 2007). Nevertheless, medical management without planned revascularization remains the initial treatment strategy for a considerable proportion of these patients (Chan et al. 2008). Observational studies have demonstrated that nearly 50% of UA/NSTEMI ACS patients in both the United States and other countries do not undergo catheterization and/or revascularization procedures during the initial hospitalization (Goldberg et al. 2004; Carruthers et al. 2005; Roe et al. 2005; Mandelzweig et al. 2006; Tricoci et al. 2006a). Similar patterns of invasive procedure use (GUSTO IIb 1996; PURSUIT 1998; Goodman et al. 2000; Yusuf et al. 2003; Blazing et al. 2004; Fox et al. 2004; Yusuf et al. 2006) are demonstrated in recent UA/NSTEMI ACS clinical trials where the decision for angiography and revascularization was not dictated by protocol. The prognosis for medically managed patients, excluding those with insignificant coronary artery disease (CAD), is poor compared with those treated with early revascularization. There is an inverse relationship between the predicted risk of adverse outcomes and the decision for invasive cardiac procedures, which are typically concentrated in the patients who are at lowest risk of mortality and recurrent myocardial infarction (Fox et al. 2007[b]).

Regrettably, the treatment options available for the medically managed population are limited. Many of these patients have contraindications to revascularization, or revascularization may be technically impossible because of anatomically advanced CAD. Data from the “Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation (CRUSADE)” initiative of the American College of Cardiology (ACC) and American Heart Association (AHA) Guidelines, implemented largely in tertiary hospitals in the United States, showed that approximately 25% of patients with NSTEMI ACS in contemporary United States practice were considered to have contraindications to cardiac catheterization, with the most frequent types of documented contraindications related to medical co-morbidities (Mehta et al. 2006).

1.2.2. Dual Antiplatelet Therapy in the Medical Treatment of ACS

Contemporary randomized clinical trials evaluating UA/NSTEMI ACS patients have not focused specifically on medically managed patients. Consequently, the current practice guidelines do not clearly delineate treatment approaches specifically for medically managed patients (Anderson et al. 2007; Bassand et al. 2007). While superficially appealing, encouraging the broader use of evidence-based medications for medically managed patients is unwarranted without proof of efficacy in a population that is at high risk of drug-related toxicity. As such, several evidence-based medications that have proven efficacious in highly-selected, low-risk clinical study populations require further study in the medically managed population.

The current standard of care for all patients with UA/NSTEMI ACS, not just those who undergo PCI, includes dual antiplatelet therapy with aspirin and a thienopyridine in both the acute and chronic phases of treatment (Anderson et al. 2007; Bassand et al. 2007; Yusuf et al. 2001). Of the currently approved thienopyridines, clopidogrel has largely replaced ticlopidine because of its once-daily dosing regimen, improved tolerability, and lowered incidence of adverse hematologic side effects (Meadows and Bhatt 2007). Despite being superior to aspirin alone in suppressing ischemic events in a heterogeneous population of NSTEMI ACS patients that included both revascularized and medically managed patients, dual antiplatelet therapy is under-utilized in the medically managed patient (Bhatt et al. 2004; Tricoci et al. 2006b; Oliveira et al. 2007).

The optimal timing of initiation of clopidogrel therapy in medically managed UA/NSTEMI patients, especially those who undergo angiography before the final decision for medical management is made, remains uncertain and has been shown to be highly variable across centers, countries, and regions (Fox et al. 2007[b]; Alexander et al. 2008). The 2007 ACC/AHA UA/NSTEMI guidelines endorse a Class I recommendation for the use of either clopidogrel or an intravenous glycoprotein IIb/IIIa inhibitor upstream before diagnostic angiography for patients who are planned for early catheterization to guide the revascularization strategy (Anderson et al. 2007). In contrast, the 2007 ESC UA/NSTEMI guidelines recommend a policy of routine upstream clopidogrel before angiography for all patients who are intended to undergo early angiography (Bassand et al. 2007). Due to concerns related to peri-operative bleeding risks during CABG for patients who receive clopidogrel before angiography and then are determined to need surgical revascularization, and the desire to avoid a 4-5 day waiting period between angiography and surgery (to allow for a washout of the anti-platelet effect of clopidogrel), many centers prefer to wait until obtaining definition of the coronary anatomy during angiography before administering a clopidogrel loading dose (Fox et al. 2004; Alexander et al. 2008). As a result of these issues and the ambiguities of practice guidelines recommendations for early clopidogrel use before angiography, there may be a reasonable, evidence-based upper limit of 72 hours before a clopidogrel loading dose is administered since this is the upper time range specified by the ACC/AHA/ESC

guidelines for performing early cardiac catheterization (Anderson et al. 2007; Bassand et al. 2007).

While an incremental benefit of dual antiplatelet therapy with clopidogrel over aspirin alone has been demonstrated, limitations of clopidogrel, such as variability and extent of platelet inhibition, may explain, in part, why atherothrombotic events continue to occur in some patients (Angiolillo et al. 2007[a]; Geisler and Gawaz 2007; Maree and Fitzgerald 2007; Siller-Matula et al. 2007; Gurbel and Tantry 2006). Several small studies have associated thrombotic complications in ACS and PCI with poor antiplatelet response to the approved standard clopidogrel dosing regimen (300-/75-mg LD/MD) (Matetzky et al. 2004; Gurbel et al. 2003; Gurbel et al. 2005; Barragan et al. 2003; Cuisset et al. 2006). Additionally, other studies have demonstrated benefit from using higher than approved doses of clopidogrel (Patti et al. 2005; Hochholzer et al. 2006; Montalescot et al. 2006; Buonamici et al. 2007; Angiolillo et al. 2007[b]; Chan et al. 2007). These observations suggest the possibility that the higher and more consistent levels of platelet inhibition that can be achieved with prasugrel also may improve clinical outcomes in the medically managed patient, as has been shown for ACS patients undergoing PCI (Wiviott et al. 2007[a]).

1.2.3. TRILOGY ACS: Evaluating Unanswered Questions in the Medically Managed UA/NSTEMI ACS Population

In TRILOGY ACS, the balance between treatment benefit and the risk of bleeding will be further explored. This is important to understand, as the medically managed population is expected to have an increased risk of bleeding with antithrombotic therapy because their multiple medical co-morbidities affect drug metabolism and clearance (Alexander et al. 2007). In the TRITON-TIMI 38 Study, superior efficacy of a more potent P2Y₁₂ inhibitor in attenuation of ischemic events was accompanied by a significant increase in bleeding.

While overall non-CABG-related bleeding was higher in prasugrel versus clopidogrel treated subjects in TRITON, three specific subgroups are pertinent to design considerations for TRILOGY ACS: subjects with a history of stroke or transient ischemic attack before enrollment, the elderly \geq age 75, and those with a body weight of less than 60 kg (Wiviott et al. 2007[a]). Each of these patient characteristics are known to be associated with an increased risk of adverse outcomes from the use of antiplatelet or antithrombotic agents (Mahaffey et al. 1999; Alexander et al. 2005). An increased risk of adverse outcomes with dual-antiplatelet therapy has also been reported in recent studies of subjects with a history of stroke (Fintel 2007), thus justifying exclusion of these subjects from TRILOGY ACS. In TRITON, the increased risk of non-CABG-related TIMI bleeding in subjects <60 kg or ≥ 75 years of age appeared to be associated with increased exposure to prasugrel active metabolite. TIMI major or minor bleeding was lower in the first exposure quartile than in the upper quartiles. More than 60% of subjects ≥ 75 years of age had active metabolite exposure in the 3rd and 4th exposure

quartiles. Furthermore, fatal bleeds in these subjects could not be explained by low body weight or a TIA/stroke history. Therefore, based on TRITON data, prasugrel dose reduction in TRILOGY ACS which reduces active metabolite exposure down to first quartile range would be expected to reduce bleeding risk in this study.

Another gap in the knowledge continuum is the optimal duration of chronic therapy with P2Y₁₂ inhibitors as subjects with UA/NSTEMI ACS transition from acute to stable disease. CURE provides evidence of benefit up to 12 months. However, in the CHARISMA study, which enrolled a broad population with either clinically evident cardiovascular (CV) disease or multiple CV risk factors for a median study treatment of 28 months, the use of clopidogrel and aspirin was not more effective than aspirin alone and was associated with a higher risk of moderate bleeding (Bhatt et al. 2006). A post-hoc analysis of the higher-risk secondary prevention subgroup of CHARISMA (Bhatt et al. 2007) did show a statistically significant reduction in the composite of CV death, myocardial infarction (MI), and stroke with a similar bleeding profile to the overall study. Thus, further investigation of the effect of long-term dual antiplatelet treatment in TRILOGY ACS appears to be justified.

The final justification for TRILOGY ACS is the unmet need for mechanistic data in Phase 3 clinical trials (Sabatine et al. 2006). A large sample of the study population will provide data on platelet function and genomic variations relevant to thienopyridine metabolism that could substantiate the clinical effects noted in the study. While not feasible with traditional light transmission aggregometry (LTA) methods, platelet aggregation can now be measured in large clinical trials with a recently approved point of care device, the Accumetrics VerifyNow® system (Price et al. 2006; van Werkum et al. 2006; Malinin et al. 2007). Thus, this study should provide valuable insights regarding biological interactions between subject and drug that may be useful in determining the validity of specific subgroup analyses in a large outcomes trial and in developing tailored therapy (Ginsburg et al. 2005).

1.2.4. Conclusions

Based upon the significant number of subjects with UA/NSTEMI ACS who are managed medically and their high risk for future cardiovascular events, further exploration of novel treatment strategies for this population, who are under-represented in large clinical trials, is warranted. In studies thus far, prasugrel has shown promising benefits in comparison with clopidogrel, including higher and more consistent attenuation of platelet aggregation with less variability in patient response (Jernberg et al. 2006; Brandt et al. 2007). Thus, with its superior antiplatelet profile, prasugrel should improve cardiovascular outcomes in medically managed subjects through reduction in atherothrombotic events. TRILOGY ACS is proposed to assess cardiovascular outcomes when study treatment with prasugrel or clopidogrel is initiated within 10 days of UA/NSTEMI ACS presentation. Specifically, the TRILOGY ACS study will determine whether prasugrel and aspirin is a superior treatment strategy compared to the current

standard of care, clopidogrel and aspirin, for long-term treatment of medically managed UA/NSTEMI ACS subjects.

Clinical development of prasugrel is a co-development project between Daiichi Sankyo Pharma Inc. (hereafter referred to as Daiichi Sankyo) and Eli Lilly and Company (hereafter referred to as Lilly). More detailed information about the known benefits and risks of prasugrel may be found in the Investigator's Brochure.

2. Objectives

2.1. Primary Objective

The primary objective of this study is to test the hypothesis that prasugrel and aspirin is superior to clopidogrel and aspirin in the treatment of medically managed subjects enrolled within 10 days of the unstable angina/non-ST-segment elevation myocardial infarction (UA/NSTEMI) index event. Superiority will be assessed by the reduction in risk of the composite endpoint of first occurrence of cardiovascular (CV) death, myocardial infarction (MI), or stroke throughout the study.

The primary analysis will be conducted in a hierarchical manner, with evaluation of the primary endpoint performed first in medically managed UA/NSTEMI subjects < age 75 years. Conditional on successfully establishing superiority in the primary analysis, the same composite endpoint will be evaluated in the entire population.

2.2. Secondary Objectives

The following secondary endpoints will be analyzed in both the population of medically managed UA/NSTEMI subjects age <75 years and the entire medically managed UA/NSTEMI population (subjects < age 75 years and subjects \geq age 75 years).

2.2.1. Efficacy Objectives

The secondary efficacy objectives are to compare the prasugrel and clopidogrel groups with respect to:

- The risk of the composite endpoint of first occurrence of CV death and MI.
- The risk of the composite endpoint of first occurrence of CV death, MI, stroke, or rehospitalization for recurrent UA.
- The risk of the composite endpoint of first occurrence of all-cause death, MI, or stroke.
- Stent thrombosis.

Components of the primary and secondary composite endpoints will also be analyzed individually as described in Section 8.2.6 and Section 8.2.7, respectively.

2.2.2. Safety Objectives

In subjects receiving prasugrel or clopidogrel, the safety objectives are to evaluate the incidence of:

- Non-coronary artery bypass graft (non-CABG)-related life-threatening bleeding (a subset of the Thrombolysis in Myocardial Infarction [TIMI] major bleeding).
- Non-CABG-related TIMI major bleeding (see Section 6.3.1).
- Non-CABG-related TIMI major or minor bleeding.
- Non-CABG-related TIMI major, minor, or minimal bleeding.
- Non-CABG-related Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) severe or life-threatening bleeding (see Section 6.3.1).
- Non-CABG-related GUSTO severe or life-threatening bleeding or moderate bleeding.
- Non-CABG-related GUSTO severe or life-threatening, moderate, or mild bleeding.
- Fatal bleeding or intracranial hemorrhage (ICH).
- CABG-related bleeding.

AND

- To evaluate the overall safety and tolerability (based on vital signs, laboratory values, non-benign neoplasms, the occurrence of treatment-emergent adverse events including adverse events meeting the regulatory definition of a serious adverse event, and those events leading to permanent discontinuation of study drug) in subjects receiving prasugrel or clopidogrel.

2.3. Substudy Objectives

Two substudies will be performed in Study TABY. The first substudy will investigate pharmacodynamic response (platelet function), genetic variants related to drug metabolism, and biomarkers of inflammation and hemodynamic stress. The second substudy will investigate health outcomes. Both cohorts (population <75 years of age and the population ≥75 years of age) will be eligible for participation in these substudies.

2.3.1. Platelet Function Substudy

Subjects who participate in the platelet function substudy will be assessed for each of the substudy objectives discussed in Section 2.3.1.1 through Section 2.3.1.3 below.

2.3.1.1. Pharmacodynamic Objectives

Platelet aggregation will be measured by the Accumetrics VerifyNow® P2Y₁₂ and aspirin assays. The key platelet function objectives are:

- To demonstrate a lower risk of the composite endpoint of CV death, MI, or stroke in subjects with greater attenuation of platelet aggregation, irrespective of baseline treatment.
- To compare the prasugrel and clopidogrel groups with respect to degree of platelet aggregation.
- To compare the prasugrel and clopidogrel groups with respect to intra- and inter-subject variability in platelet aggregation during maintenance dosing.
- To assess the incidence of bleeding events by degree of platelet aggregation.

2.3.1.2. Genomic Objectives

Genomic substudy objectives are:

- To assess the interaction between treatment groups and the presence of genetic variation in drug metabolizing enzymes and transporters on platelet function.
- To assess the interaction between treatment group and the presence of genetic variation in drug metabolism enzymes and transporters on clinical efficacy and/or safety outcomes.

2.3.1.3. Other Objectives

Other substudy objectives are:

- To assess the effect of the prasugrel and clopidogrel groups on biomarkers of inflammation (high-sensitivity C-reactive protein [hsCRP]) and hemodynamic stress (N-terminal prohormone brain natriuretic peptide [NT-proBNP] or brain natriuretic peptide [BNP]).

2.3.2. Health Outcome Substudy Objectives

Health outcome objectives are:

- To compare the prasugrel and clopidogrel treatment arms with respect to:
 - a) Major healthcare resource use, cumulative medical costs, and incremental cost effectiveness.
 - b) Health-related quality of life.
- To examine healthcare costs and resource use as a function of both treatment assignment and degree of platelet aggregation.

2.4. Other Objectives

Other prespecified and exploratory analyses will be conducted, as specified in the statistical analysis plan (SAP), to include repeating the primary and all secondary analyses in the age ≥ 75 years population.

3. Investigational Plan

3.1. Summary of Study Design

Study H7T-MC-TABY (TRILOGY ACS) is a Phase 3, multicenter, randomized, parallel-group, double-blind, double-dummy, active-controlled study. Eligible subjects will be those with recent (within 10 days) UA/NSTEMI (index event) who are to be medically managed. The study population will be initially stratified into two cohorts on the basis of age. The primary analysis population will consist of subjects <75 years of age, while subjects ≥ 75 years of age will be treated as a separate cohort.

Eligibility for this study will be determined by both the timing of the medical management decision and by commercial clopidogrel status at the time of randomization.

Subjects will be randomized within 10 days of the onset of the UA/NSTEMI index event once the decision for a medical management strategy can be made with reasonable certainty; that is, coronary revascularization is not planned for management of the index event (see Section 4.1.1 for details defining onset of the index event). The clinical evaluation upon which this decision is based will be at the discretion of the investigator. This may include the results of coronary angiography performed within 10 days of the onset of the index event, results of prior coronary diagnostic evaluation, and/or other subject clinical characteristics such as and co-morbidities which may preclude revascularization.

For subjects with a medical management decision who are randomized beyond 72 hours of onset of the index event, commercial clopidogrel must have been received no later than 72 hours following the onset of the index event (as defined in Section 4.1.2). For subjects whose medical management decision and randomization occurs no later than 72 hours following the onset of the index event, prior clopidogrel treatment is not a consideration for eligibility.

Subjects will be randomly assigned in a 1:1 ratio to study treatment with either prasugrel or clopidogrel, both of which will be administered on a background of low-dose aspirin. If the subject is receiving commercial clopidogrel treatment at the time of randomization, this will be discontinued. Subjects who are randomized less than 72 hours following the onset of the index event and who are not receiving commercial clopidogrel, or who received clopidogrel but are not deemed to be at steady state, will receive a loading dose of the randomized treatment (prasugrel or clopidogrel) followed by a maintenance dose as detailed below. Subjects who are receiving commercial clopidogrel at the time of randomization and are considered to be at steady state will be switched to a maintenance dose of either prasugrel or clopidogrel and will not receive a loading dose. The randomized maintenance dose of prasugrel will differ based upon age and body weight at the time of randomization as described below.

After initial stratification by age, randomization of subjects to the two treatment groups will be stratified as described in Table TABY.1 below. This stratification is being performed so that any possible bias related to switching subjects with prior commercial clopidogrel exposure to prasugrel may be evaluated.

Table TABY.1. Study Drug Treatment by Commercial Clopidogrel Status

Medically Managed UA/NSTEMI Subjects	
Commercial Clopidogrel Status at Time of Randomization	Randomized Treatment
Stratum 1 Either clopidogrel-naïve or not at steady state ^a on commercial clopidogrel, with a decision for medical management and randomization within 72 hours following onset of the index event.	Loading Dose/Maintenance Dose: Clopidogrel 300- mg loading dose followed by 75-mg once-daily maintenance dose <u>or</u> prasugrel 30-mg loading dose followed by 5 / 10- mg once-daily maintenance dose ^b (each administered on a background of low-dose aspirin).
Stratum 2 Commercial clopidogrel loading dose of at least 300 mg administered within 72 hours following onset of the UA/NSTEMI index event with administration of daily maintenance dose thereafter.	Maintenance Dose Only: Clopidogrel 75-mg once-daily maintenance dose <u>or</u> prasugrel 5 / 10-mg once-daily maintenance dose ^b (each administered on a background of low-dose aspirin).
Stratum 3 Commercial clopidogrel treatment prior to the index event and the subject deemed to be at steady state at the time of the onset of the index event; and MD maintained up until time of randomization.	

^a Subjects defined as clopidogrel-naïve or not at steady state are those subjects who:

- (i) have not received clopidogrel prior to the index event or have received a maintenance dose of commercial clopidogrel for <5 consecutive days immediately prior to the index event, AND
- (ii) have NOT received a commercial clopidogrel loading dose within 72 hours following the onset of the index event.

^b Subjects >75 years of age or <60 kilograms of body weight will receive the 5-mg maintenance dose.

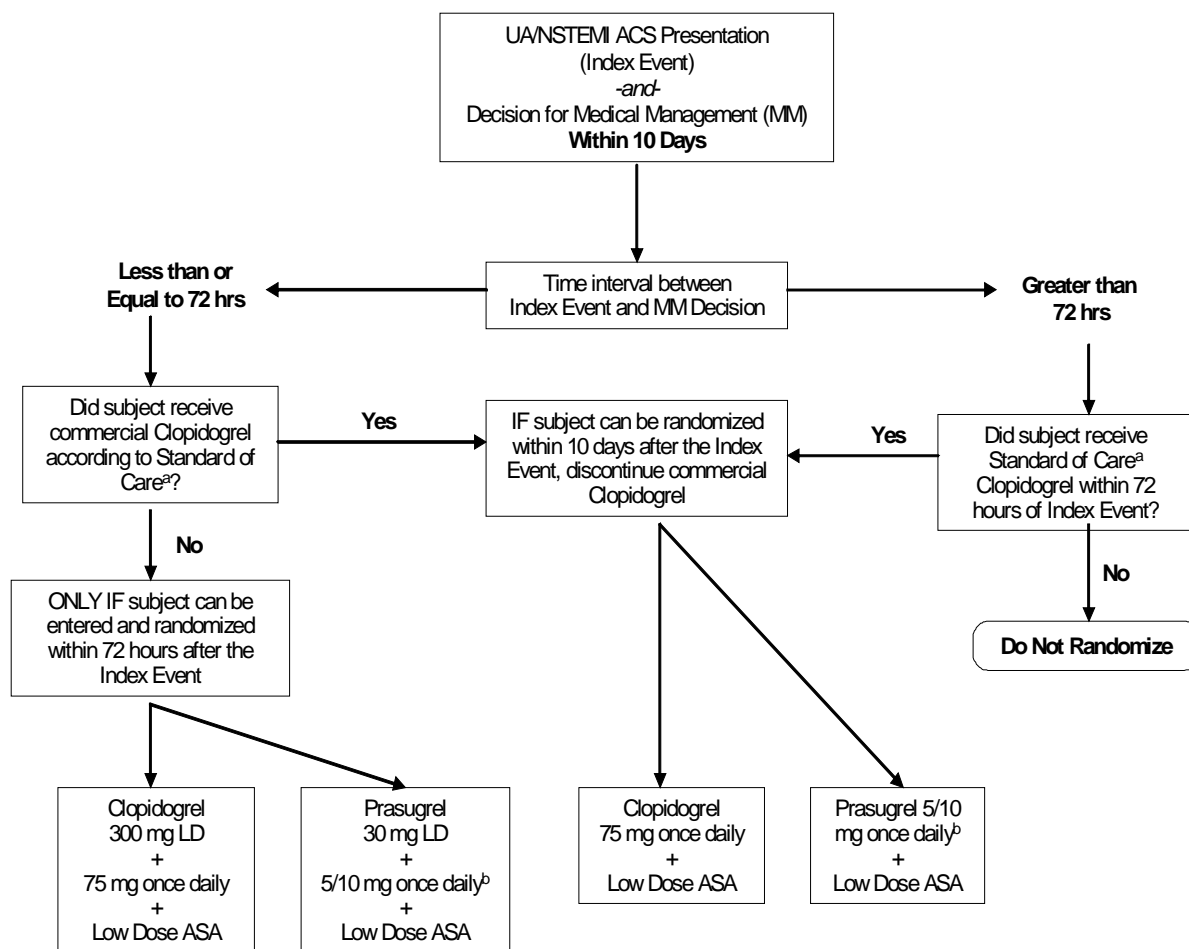
The study will continue until the following are attained:

- An estimated 688 subjects <75 years of age have experienced an adjudicated event of the composite triple endpoint of CV death, MI, or stroke.
- All subjects <75 years of age have either completed at least 6 months of follow-up (completion of Visit 5 per study schedule) or discontinued before 6 months of follow-up.
- At least 2000 subjects ≥ 75 years of age have been randomized into the study, with the last subject having either completed at least 3 months of follow-up (completion of Visit 4 per study schedule) or discontinued before 3 months of follow-up.

The total study population of approximately 10,300 subjects will be enrolled at an estimated 800 sites globally (7800 subjects <75 years of age and a maximum enrollment of 2500 subjects ≥ 75 years of age). A Study Operations Committee (SOC) will monitor the proportion of subjects who meet the primary endpoint. If this blinded review indicates that the event rate is different from expected, the SOC will recommend modifying the number of subjects randomized.

It is intended that subjects remain on study drug for a maximum of 30 months or until completion of the study, whichever time is earlier. A rolling close out will be performed over a 3-month period.

The subject eligibility and treatment algorithm is shown in Figure TABY.1 below. The study design and timeline are illustrated in Figure TABY.2. Refer also to Attachment TABY.1 (Study Schedule) and Attachment TABY.2 (Clinical Laboratory Tests) for more information on timing and details of study procedures.



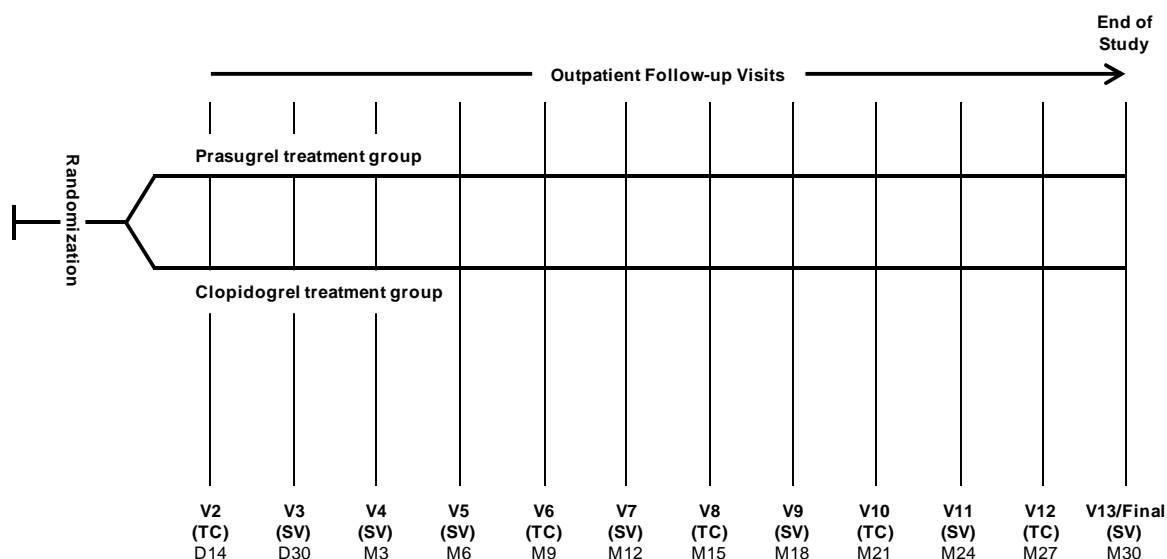
^a Standard of Care defined as:

- Subjects receiving commercial clopidogrel LD within 72 hours after the index event, followed by daily clopidogrel 75 mg MD.
- Subjects receiving commercial clopidogrel MD for greater than or equal to 5 days prior to the Index Event and daily until randomization.

^b Subjects ≥ 75 years of age or < 60 kilograms of body weight will receive the 5-mg maintenance dose.

Abbreviations: ACS = acute coronary syndromes; ASA = aspirin; hrs = hours; LD = loading dose; MD = maintenance dose; MM = medical management; NSTEMI = non-ST-segment elevation myocardial infarction; UA = unstable angina.

Figure TABY.1. Subject eligibility and treatment algorithm for Protocol H7T-MC-TABY.



Abbreviations: SV = site visit; TC = telephone contact.

Visit windows are for Visits 2 and 3, ± 3 days; Visit 4, ± 7 days; Visits 5 up to Final Visit, ± 14 days.

Figure TABY.2. Study visit schedule for Protocol H7T-MC-TABY (follow-up Visits 2 through 13).

Subjects presenting with recent (within 10 days) UA/NSTEMI (see Section 4.1.1 for disease diagnostic criteria) who are planned to be medically managed may be considered for entry (that is, may sign informed consent) into this study. The following information obtained as part of routine medical care, if available, should be reviewed to determine a subject's eligibility for entry: medical history and prior clopidogrel treatment, physical examination, standard 12-lead ECG, and laboratory values, including troponin I or troponin T, or creatine kinase-MB fraction (CK-MB). Total CK may be used if troponin and CK-MB are unavailable.

Following screening and the completion of informed consent, eligible subjects will be assigned randomly (that is, enrolled) to treatment with either prasugrel or clopidogrel in a 1:1 ratio via an interactive voice response system (IVRS). The subject, as well as all site personnel, will be blinded to study drug. The study will employ a double-dummy design: subjects will receive active formulation of one drug and placebo formulation of the other for the loading dose and maintenance doses. Subjects will be randomized at the country level, with stratification by age and commercial clopidogrel status (see Table TABY.1 for the stratification by commercial clopidogrel status).

At a subset of study sites, after randomization, but prior to receiving the first dose of study drug, baseline platelet function will be measured using the Accumetrics VerifyNow® P2Y₁₂ assay. Platelet aggregation will be measured again 120 ± 10 minutes

after the first dose. Aspirin response will be assessed using the VerifyNow Aspirin assay in the same subset of study sites, as outlined in Attachment TABY.1 (Study Schedule) and Attachment TABY.2 (Clinical Laboratory Tests). Results of the P2Y₁₂ assay will be encrypted.

All subjects are to be treated with adjunctive aspirin (open-label and commercially available), not to exceed 162 mg, for the duration of the study. A low, daily concomitant aspirin dose between 75 and 100 mg is strongly recommended. The dose may be increased to a maximum of 325 mg in subjects undergoing PCI during follow-up for a period of time as determined by the investigator based on the subject's individual clinical circumstances.

Subjects participating in the platelet function substudy should take their daily dose of study drug at least 2 hours prior to the planned outpatient visits. Clinical history, central laboratory testing, ECGs, and measurement of platelet function (at a subset of sites) will be obtained during outpatient visits, as outlined in Attachment TABY.1 (Study Schedule).

Based on the known pharmacology of prasugrel and clopidogrel, study drug should be discontinued prior to elective surgical and invasive procedures. If the subject has an elective surgical procedure, including CABG, the study drug should be temporarily discontinued at least 7 days before surgery. This recommendation is based on the pharmacological effect of prasugrel determined in clinical pharmacology studies and the clinical observations in the TRITON-TIMI 38 study. Study drug should be restarted when, in the investigator's opinion, it is safe to do so. Please refer to Section 4.3.2 for recommendations regarding patient management and study drug discontinuation for urgent surgical and invasive procedures for which study drug cannot be temporarily discontinued at least 7 days before the surgery or procedure.

If a subject experiences recurrent ischemic symptoms after randomization, clinical evaluation and treatment (including the potential need for angiography and revascularization procedures) will be left to the investigator's or treating physician's discretion. Every effort should be made to obtain all pertinent information, including clinical findings, local laboratory values, and ECGs from the treating facility.

Subjects who permanently discontinue study drug prior to completing the study should have an on-site visit performed as soon as possible and will remain in the study to be evaluated for efficacy and safety endpoints. Adverse events, serious and non serious, will be collected for 30 days after the last dose of study drug. Thereafter, serious adverse events will only be reported if the investigator feels the events were related to either study drug or a protocol procedure. Subjects should return for the on-site Final Visit. If a subject is unwilling or unable to return for on-site visits, sites should still attempt to collect as much visit information as possible through telephone contact.

If a subject withdraws participation from the study or is lost to follow-up, his or her vital status will be checked within the three months of the study closure by consultation of available public sources, as allowed by local regulations.

3.1.1. Study Operations and Medical Oversight

The sponsor will assign the obligation of study operation management to a contract research organization (CRO). The sponsor will assign the obligation of medical and scientific oversight to an academic research organization (ARO), Duke Clinical Research Institute (DCRI).

A 24-hour global Helpline will be established to ensure that medical questions and study operational questions can be answered by the ARO and the CRO. Throughout the study, the CRO and the ARO will maintain call logs where all issues and resolutions will be documented when a site is assisted.

All participating investigators and site staff will be provided the CRO Helpline contact information and instructed to direct all calls to the CRO Helpline as the primary point of contact. The CRO will triage calls and direct investigators and site staff as appropriate.

Additional study oversight will be provided by an Executive Committee and a Steering Committee. The members of the Executive Committee will serve as high level advisors of the overall conduct of the study, in conjunction with the Sponsor. The Steering Committee will assist in the conduct of the study and, in particular, assist with local issues to support the good implementation and conduct of the study worldwide.

3.2. Discussion of Design and Control

The primary objective of this study is to test the hypothesis that prasugrel and aspirin is superior to clopidogrel and aspirin in subjects whose study treatment is initiated within 10 days of the index UA/NSTEMI event, when medical management, without acute coronary revascularization, has been determined to be the best therapeutic option.

Even though data show that elderly subjects benefit the most from an early invasive strategy, subjects age 75 or older are more likely to be medically managed than younger subjects. According to recent registries (Bhatt et al. 2004), approximately 40-50% of these subjects are medically managed (www.crusadeqi.com).

In TRILOGY ACS, while the primary endpoint will first be tested in subjects less than 75 years old, particular emphasis has been put into studying subjects age 75 and older. Elderly subjects are often either excluded from clinical studies or under represented. TRILOGY ACS will ensure that a sufficient number of elderly subjects are studied as at least 2000 (maximum 2500) subjects age 75 or older will be randomized as a separate cohort. This design maintains the balance between the two treatment groups. Conditional on successfully establishing superiority of prasugrel over clopidogrel in subjects <75 years of age, treatment groups will be compared on all randomized subjects

(including subjects <75 years of age and ≥ 75 years of age). Analyses in the cohort age 75 years or older alone will be conducted as pre-specified exploratory analyses.

Superiority will be assessed by the reduction in risk of the composite triple endpoint of CV death, MI, or stroke, the same primary efficacy endpoint used in the CURE study (Yusuf et al. 2001). Subgroup analyses from the CURE (Yusuf et al. 2001) and CHARISMA studies (Bhatt et al. 2007) and results from the CREDO study (Steinhubl et al. 2002) suggest a long-term treatment effect with aspirin and clopidogrel that extends beyond the period of hospitalization, which appears to be enhanced in UA/NSTEMI subjects, regardless of whether acute coronary revascularization has been performed. In order to assess long-term clinical outcomes, treatment in TRILOGY ACS will be continued for a median duration of at least 18 months. This same composite triple endpoint was studied in the previously mentioned TRITON-TIMI 38 Study. The subject population in TRILOGY ACS is also similar to TRITON-TIMI 38, except that ST-segment elevation myocardial infarction (STEMI) subjects will not be included and subjects will not undergo PCI as initial or planned treatment for their index event.

The subject population for this study will consist of intermediate to high-risk medically managed subjects presenting within 10 days of the onset of their UA/NSTEMI index event. The 10-day enrollment window following the onset of the index event should ensure that the investigator has enough time to determine, with reasonable certainty, that a medical management strategy (no acute coronary revascularization) is the best decision for a given subject. Enrollment eligibility within this 10-day period will be determined both by the timing of the decision for medical management and prior commercial clopidogrel treatment. The subject will either receive clopidogrel treatment (either initiated with a LD or at steady-state on MD treatment initiated prior to the index ACS event) within 72 hours of the index UA/NSTEMI event or will be eligible for randomization within 72 hours. In many study centers, particularly those in the US, clopidogrel is administered later than 24 hours from the index event. This is due, at least in part, to the desire at some centers for coronary angiography prior to administering clopidogrel. (See Section 1 for more details.)

The study treatment that subjects receive will depend upon whether they are expected to be at steady state level on commercial clopidogrel at time of randomization. A steady-state level of platelet inhibition with clopidogrel is achieved within 5 days at doses of 75 mg per day or within 24 hours of a 300 mg loading dose (Thebault et al. 1999); therefore, subjects who have received either (i) ≥ 5 consecutive days commercial clopidogrel immediately prior to the index event or (ii) a commercial clopidogrel loading dose of at least 300 mg within 72 hours following the onset of the index event (followed by once-daily 75 mg maintenance dose) are expected to be at pharmacodynamic steady state on clopidogrel at the time of randomization. This group does not require a loading dose of study drug, and will be randomized to once-daily maintenance doses of clopidogrel (75 mg) or prasugrel (5 or 10 mg). Subjects who are either clopidogrel-naïve or deemed not to be at steady state and are enrolled within 72 hours following the index event will be

randomized to a loading dose of clopidogrel (300 mg) or prasugrel (30 mg) followed by once-daily maintenance doses of clopidogrel (75 mg) or prasugrel (5 or 10 mg), respectively. (See Section 5.4 and Protocol Attachment TRILOGY ACS.5 for study treatment rationale).

There are limited data on initiation of prasugrel in subjects already on clopidogrel. However, in Study H7T-EW-TABF (a Phase 1 study to assess the effect of switching from clopidogrel to prasugrel on platelet aggregation in healthy subjects), no safety concerns were observed when either a 60-mg prasugrel loading dose or a 10-mg maintenance dose was administered immediately following 11 days of clopidogrel maintenance treatment. Thus, switching subjects from clopidogrel to prasugrel in TRILOGY ACS is not expected to raise any safety concern. As a safeguard, a Data Monitoring Committee (DMC) will monitor the safety of all subjects during the course of the study.

4. Study Population

4.1. Inclusion Criteria

Before entering the study, informed consent must be signed by the study participant according to local rules and regulations. Subjects are eligible to be entered in the study (that is, sign informed consent) only if they are of a legal age (at least 18 years of age) and competent mental condition to provide written informed consent, and meet all of the following criteria:

- [1] Have had a UA/NSTEMI index event within 10 days (240 hours) prior to randomization (based on the disease diagnostic criteria in Section 4.1.1).
- [2] Have had a medical management strategy decision made with reasonable certainty; that is, neither PCI nor CABG is planned for treatment of the index event.
 - For subjects whose medical management decision and randomization occurs no later than 72 hours following onset of the index event, prior clopidogrel treatment is not a consideration for eligibility.
 - For subjects with a medical management decision who are randomized beyond 72 hours of onset of the index event, clopidogrel must be administered according to standard of care practice for ACS patients no later than 72 hours following the onset of the index event (as defined in Section 4.1.2).
- [3] Have had at least 1 of the following 4 high-risk features at the time of the UA/NSTEMI event:
 - Age ≥ 60 years
 - Prior MI evidenced by pre-existing Q waves, or demonstration of infarction on imaging studies, or prior documentation of elevated cardiac markers.
 - Diabetes Mellitus - defined by concomitant treatment with an oral hypoglycemic agent and/or insulin.
 - Coronary revascularization (either PCI or CABG) at least 30 days **before** the onset of the index ACS event.
- [4] Deleted; replaced with new Exclusion Criterion [39].

4.1.1. Disease Diagnostic Criteria

4.1.1.1 Definition of UA/NSTEMI

For purposes of this study, recent UA/NSTEMI will be defined as follows:

- NSTEMI is defined as a history of chest discomfort or anginal-equivalent symptoms of ≥ 5 minutes duration at rest within 24 hours prior to the index event, with no evidence of persistent ST-segment elevation. Subjects must also have a CK-MB or troponin T or I greater than the upper limit of normal (ULN) defined by the local laboratory assay. If CK-MB or troponin are not available, total CK ≥ 2 times ULN is acceptable.
- UA is defined as a history of chest discomfort or anginal-equivalent symptoms of ≥ 5 minutes duration at rest within 24 hours prior to the index event, with ST-segment depression >1 mm in at least two or more ECG leads without elevation of CK-MB, troponin T, or troponin I.

The onset for the index event will be the first medical contact for evaluation of UA/NSTEMI symptoms. First medical contact is defined as the date and time of first contact with medical personnel for the index event including Emergency Medical Systems (EMS) responders for pre-hospital evaluation, Emergency Room personnel for the initial hospital evaluation, or other medical personnel for other locations of first evaluation. If the subject was already hospitalized at the time of the UA/NSTEMI symptoms, the onset of the index event will be the date and time when the subject is initially evaluated for UA/NSTEMI (that is, when ECG or biomarkers for myocardial damage are first obtained), provided that the subject meets all other inclusion and exclusion criteria.

4.1.1.2 Decision for Medical Management

The information upon which the medical management decision is made will be at the discretion of the investigator. Any testing, which may include coronary angiography or other diagnostic evaluations for the index ACS event, must be performed within 10 days of the onset of the index event (that is, first medical contact for evaluation of UA/NSTEMI symptoms).

4.1.2. Standard of Care for Commercial Clopidogrel Use in UA/NSTEMI Subjects

Standard of care for the use of commercial clopidogrel in UA/NSTEMI subjects in this study is defined as:

- For clopidogrel-naïve subjects, treatment initiation with a clopidogrel loading dose of at least 300 mg within 72 hours following the onset of the index event followed by once-daily 75-mg maintenance dose until randomization.
- For subjects on commercial clopidogrel treatment prior to the index event, continue the once-daily 75-mg maintenance dose until randomization.

4.2. Exclusion Criteria

Subjects may not be entered into the study if they meet **any** of the following criteria:

Cardiovascular Exclusion Criteria

- [5] Decision for medical management > 72 hours after the onset of the index event without commercial clopidogrel treatment within 72 hours following the onset of the index event (Note: commercial clopidogrel treatment must continue daily thereafter until randomization).
- [6] Planned PCI or CABG as treatment for the index ACS event – either during the index hospitalization or thereafter.
- [7] PCI or CABG performed within the previous 30 days.
- [8] STEMI as the index event.
- [9] Cardiogenic shock within the previous 24 hours (defined as a systolic blood pressure <90 mm Hg associated with clinical evidence of end-organ hypoperfusion, or hypotension requiring vasopressors to maintain systolic blood pressure over 90 mm Hg and associated with clinical evidence of end-organ hypoperfusion).
- [10] Refractory ventricular arrhythmias within the previous 24 hours.
- [11] Symptoms of New York Heart Association (NYHA) Class IV congestive heart failure (CHF) within the previous 24 hours (see Attachment TABY.4 for NYHA CHF classifications).

Note: See also Exclusion Criterion [39]

Exclusion Criteria Related to Bleeding

- [12] Contraindicated for antiplatelet therapy.
- [13] Received fibrinolytic therapy as initial treatment for the index event.
- [14] Any history of bleeding diathesis.
- [15] Clinical findings associated, in the judgment of the investigator, with an unacceptably high risk of bleeding.
- [16] Any of the following:

- History of ischemic or hemorrhagic stroke
- Intracranial neoplasm, arteriovenous malformation, or aneurysm
- History of any TIA symptoms.

[17] International Normalized Ratio (INR) >1.5, if test is performed.

[18] Platelet count of <100,000/mm³.

[19] Anemia (hemoglobin [Hgb] <10 gm/dL).

[20] Deleted; combined with [21]

[21] History of spontaneous gastrointestinal or non-gastrointestinal internal bleeding requiring in-hospital treatment, unless the event has been definitively treated and, in the investigator's opinion, has a low likelihood of recurrence.

[22] Currently receiving hemodialysis or peritoneal dialysis.

Note: For criteria dependent on laboratory values (ie, criteria 17-19), the values obtained closest to randomization should be used to determine eligibility.

Prior/Concomitant Therapy Exclusion Criteria

[23] History of intolerance or allergy to aspirin or approved thienopyridines (ticlopidine or clopidogrel).

[24] Treated with ticlopidine within 5 days of randomization.

[25] Receiving prasugrel treatment at the time of screening.

[26] Receiving oral anticoagulants at the time of screening or are anticipated to require oral anticoagulants therapy during the course of the study.

[27] Receiving daily treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) or cyclooxygenase-2 (COX2) inhibitors that cannot be discontinued or are anticipated to require >2 weeks of daily treatment with NSAIDs or COX2 inhibitors during the study.

General Exclusion Criteria

[28] Unwilling to provide or not sufficiently mentally competent to provide written informed consent.

[29] Study site personnel directly affiliated with the study or are immediate family of study site personnel directly affiliated with the study. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

- [30] Employed by Eli Lilly and Company, Ube Industries Limited, Daiichi Sankyo Pharma Inc, the academic research organization (ARO), or the contract research organization (CRO) (that is, employees, temporary contract workers, or designees responsible for the conduct of the study). Immediate family of Lilly employees may participate in Lilly-sponsored clinical studies, but are not permitted to participate at a Lilly facility. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
- [31] Previously completed or withdrawn from this study or any other study investigating prasugrel.
- [32] Received treatment within the last 30 days with a drug or device that has not received regulatory approval for any indication at the time of study entry or are presently enrolled in another interventional drug or device study.
- [33] Females who are known to be pregnant, who have given birth within the past 90 days, or who are breastfeeding.
- [34] Females of childbearing potential (that is, females who are not surgically or chemically sterilized and who are between menarche and 1-year post menopause) and do not agree to use a reliable method of birth control during the study.
- [35] Concomitant medical illness (for example, terminal malignancy) that, in the opinion of the investigator, is associated with reduced survival over the expected treatment period.
- [36] Known severe hepatic dysfunction (that is, with cirrhosis or portal hypertension).
- [37] Conditions associated with poor treatment compliance, including alcoholism, mental illness, or drug dependence.
- [38] Unable to cooperate with protocol requirements and follow-up procedures.

Additional Cardiovascular Exclusion Criterion added in Amendment(b)

- [39] Insignificant coronary disease identified during coronary angiography performed for the index ACS event (defined as the absence of at least one stenosis in any native coronary artery visually estimated to be $\geq 30\%$).

Note: This criterion does not apply to subjects with prior percutaneous coronary intervention or prior coronary artery bypass grafting.

Note: Coronary angiography is not mandated per protocol.

4.2.1. Rationale for Exclusion of Certain Study Candidates

Exclusion criteria are grouped by category (see Section 4.2). Exclusion criteria [5] through [7] exclude subjects who have not been medically managed. Exclusion criterion [8] excludes subjects who are not in the UA/NSTEMI population. Exclusion criteria [9] through [11] exclude subjects known to have a high risk of mortality unlikely to be altered by acute or chronic thienopyridine therapy. Exclusion criteria [12] through [22] exclude subjects who are at excessive risk of bleeding complications, negatively impacting the safety of the subject. Exclusion criteria [23] through [27] exclude subjects with current or prior therapies that could negatively impact the safety of the subject or influence the analysis of the results. Exclusion criteria [28] through [30] are implementations of Good Clinical Practice (GCP) initiatives. Exclusion criteria [31] through [36] address safety concerns. Exclusion criteria [37] and [38] address efficacy and safety concerns. Exclusion criterion [39] excludes subjects with insignificant coronary artery disease.

4.2.2. Enrollment (Randomization) Criteria

Subjects entered into the study may not be enrolled (that is, randomly assigned to a treatment group) if they:

- Are discovered to have not met all the inclusion criteria.
- Have one or more exclusion criteria present at the time of randomization.
- Are pregnant as determined by a urine or serum pregnancy test obtained after consent.

Subjects not enrolled (randomized) in the study should be discontinued from further participation in the study and will be classified as screen failures. No further follow-up is required. Non-enrolled subjects will not be included in the intent-to-treat (ITT) population.

4.3. Discontinuations

4.3.1. Subjects Inadvertently Enrolled

The criteria for enrollment must be followed explicitly. In the rare case where a subject who does not meet enrollment criteria is inadvertently enrolled, the CRO 24-hour global study Helpline should be contacted within 24 hours. All medical oversight calls will be forwarded to the ARO Hotline. If it is determined after discussion with the ARO Hotline physician that, in considering subject safety, it is appropriate to continue study drug (documentation of this is necessary), the subject will continue on study drug and be monitored for all visits and testing (including laboratory measures and ECG) for the duration of the study. If after discussion with the ARO Hotline physician, it is determined that the subject should not continue study drug, study drug will be

discontinued, but the subject will remain in the study to be evaluated for efficacy and safety endpoints. Adverse events, serious and non serious, will be collected for 30 days after the last dose of study drug. Thereafter, serious adverse events will not be reported unless the investigator feels the events were related to either study drug or a protocol procedure.

4.3.2. Temporary Discontinuation of Study Drug

There may be situations in which study drug is temporarily discontinued, such as for some adverse events or surgical procedures. If the subject has an elective surgical procedure, including CABG, the study drug should be temporarily discontinued at least 7 days before surgery. These recommendations are relevant across the thienopyridine class, as these drugs are irreversibly bound to the P2Y₁₂ platelet receptor, but specifically on the pharmacological effect of prasugrel determined in clinical pharmacology studies and the clinical observations in the TRITON-TIMI 38 study. In TRITON-TIMI 38, CABG-related bleeding risk over the first 7 days after study drug discontinuation was higher for subjects treated with prasugrel versus subjects treated with clopidogrel. The increased bleeding risk is related to the irreversibility of prasugrel binding to the platelet P2Y₁₂ receptors and the higher degree of platelet inhibition with prasugrel. Thus, new platelets must be generated to restore baseline hemostasis, a process that generally takes about 7 days.

For emergency surgical procedures that do not permit discontinuation of study drug for at least 7 days prior to the surgery, platelet transfusion may be considered to prevent excessive bleeding.

If the study drug is discontinued for an elective/urgent medical or surgical procedure, it should be restarted without a loading dose when the investigator decides it is safe to do so. For periods of discontinuation that would be expected to last >14 days, the investigator should contact the CRO Helpline (who will subsequently forward the investigator to the ARO Hotline physician) to determine whether the subject should restart study drug. Every effort should be made by the investigator to maintain subjects on study drug and to restart study drug promptly after any temporary discontinuation.

It is important to note that the study drug should not be discontinued if the subject experiences the efficacy endpoints of MI or rehospitalization for recurrent UA. However, study drug should be discontinued if the subject experiences the efficacy endpoint of stroke (whether is determined to be hemorrhagic or ischemic).

4.3.2.1. Temporary Discontinuation of Study Drug due to a Bleeding Event

The investigator may temporarily discontinue study drug therapy if a subject experiences a bleeding event. The bleeding event, the treatment of the event, and any concomitant therapy provided to the subject because of the bleeding event should be documented in the case report form (CRF; see Section 6.3 for information regarding safety evaluations).

The study drug may be restarted once the event has abated and when, in the investigator's opinion, it is safe to do so (see Section 4.3.2 regarding duration of temporary study drug discontinuation). The dates of study drug discontinuation and restart should be documented in the CRF.

4.3.2.2. Study Drug Management for Percutaneous Coronary Intervention

The investigator should not temporarily discontinue study drug or administer open-label clopidogrel therapy if a subject undergoes PCI. The PCI, and any concomitant therapy (for example, GPIIb/IIIa inhibitor and/or anticoagulants) provided to the subject because of the PCI should be documented in the appropriate CRF.

If the investigator elects to temporarily discontinue study drug before or after PCI, in general, it should be restarted without a loading dose when the investigator decides it is safe to do so. If the investigator determines that there is a potential need to provide a loading dose of a thienopyridine prior to PCI (for example, the subject is temporarily off of study drug or is noncompliant with study drug), then the investigator should contact the CRO Hotline (who will forward the investigator to the ARO Hotline physician) to discuss. If after discussion with the ARO Hotline physician it is determined that a loading dose is indicated, then open-label clopidogrel may be administered with appropriate documentation in the CRF. If a loading dose of open-label clopidogrel is administered, blinded study drug (maintenance dose) should be restarted as soon as possible. Otherwise, study drug may be restarted after temporary discontinuation without a loading dose.

4.3.2.3. Temporary Discontinuation of Study Drug due to Coronary Artery Bypass Graft Surgery

The investigator should temporarily discontinue study drug therapy for at least 7 days, if possible, if a subject undergoes CABG (see Section 4.3.2. above for a more detailed recommendation). The CABG, and any concomitant therapy provided to the subject because of the CABG, should be documented in the CRF.

Study drug should be restarted without a loading dose when the investigator decides it is safe to do so. The dates of study drug discontinuation and restart should be documented in the CRF.

Questions regarding temporary study drug discontinuation and study drug restart should be called in to the 24-hour global CRO Helpline. The CRO will triage calls and direct investigators and site staff as appropriate.

4.3.2.4. Temporary Discontinuation of Study Drug due to Other Medical or Surgical Procedures

The investigator may need to temporarily discontinue study drug therapy if a subject undergoes other invasive medical or surgical procedures (that is, dental surgery, elective surgery, endoscopic biopsy, and other invasive procedures). The medical or surgical

procedure, and any concomitant therapy provided to the subject because of the procedures, should be documented in the CRF (see Section 6.3 for information regarding safety evaluations).

If the investigator elects to temporarily discontinue study drug, it should be restarted without a loading dose when the investigator decides it is safe to do so (see Section 4.3.2 regarding duration of temporary study drug discontinuation). The dates of study drug discontinuation and restart should be documented.

4.3.3. Permanent Discontinuation of Study Drug

It may be necessary for a subject to permanently discontinue study drug. Investigators should contact the CRO Helpline prior to permanent study drug discontinuation, with medical oversight questions to be forwarded to the ARO Hotline physician. After consultation with the ARO Hotline physician, if the decision is made to permanently stop study drug, then the interactive voice response system (IVRS) should be contacted.

Subjects who permanently discontinue study drug prior to completing the study should have an on-site visit performed and will remain in the study to be evaluated for efficacy and safety endpoints. Adverse events, serious and non serious, will be collected for 30 days after the last dose of study drug. Thereafter, serious adverse events will not be reported unless the investigator feels the events were related to either study drug or a protocol procedure. The procedures to follow for this on-site visit are those for the Early Discontinuation from Study Drug Visit. If a subject is unwilling or unable to return for this on-site visit, sites should still attempt to collect as much visit information as possible, including through telephone contact.

Until the Final Visit, all subjects who permanently discontinued study drug and did not withdraw participation from the study will be followed by telephone visits that will replace all future scheduled visits. These subjects should return on-site for the Final Visit. If a subject is unwilling or unable to return for this on-site visit, sites should still attempt to collect as much visit information as possible, through telephone contact.

If discontinuation is due to an adverse event, the event is to be followed according to the procedures in Section 6.3.2 of this protocol and documented in the CRF.

Some possible reasons that may lead to permanent early study drug discontinuation include:

- The subject was inadvertently randomized and in the opinion of the investigator, (after consultation with the CRO Helpline and subsequently the ARO Hotline physician), continuation of study drug is not advisable.

- In the opinion of the investigator, a bleeding episode or any other adverse event or a significant change in a laboratory value warrants permanent discontinuation of study drug therapy. Investigators are advised to call the CRO Helpline (and subsequently discuss with the ARO Hotline physician) prior to making such a decision.
- Females who become pregnant during the maintenance phase of the study will be permanently discontinued from study drug.
- The subject requests to stop study drug permanently.
- The subject study blind is broken.

4.3.4. Discontinuation from the Study

At any time during the study, the subject may withdraw their participation from the study. At the time of discontinuing from the study, the CRO Helpline and IVRS should be contacted, and, if possible, a final close-out visit should be conducted, as shown in the Study Schedule (Attachment TABY.1). The subject will be permanently discontinued both from the study drug and from the study at that time. During the 3-month close-out period, survival status will be collected within legal and ethical boundaries for all subjects randomized who withdrew participation from the study.

4.3.5. Subjects Lost to Follow-Up

A subject would be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact subjects who fail to return for a scheduled visit. Survival status will be collected within legal and ethical boundaries for all subjects randomized, including those who did not get study drug. Vital status will be searched in public sources during the 3-month close-out period. If vital status is known at the study closure visit, the subject will not be considered lost to follow-up.

4.3.6. Discontinuation of Study Sites

Study site participation may be discontinued if the sponsor, the investigator, or the Ethical Review Board (ERB) of the study site judges it necessary for any reason. Every effort will be made to redirect the subjects to another close study site.

In conjunction with the sponsor and the ARO, the Steering Committee will review on an ongoing basis the rate of revascularization after randomization at each study site to ensure that sites are following the protocol in regards to the enrollment of the appropriate medically managed subjects. The Steering Committee may recommend discontinuation of study sites who do not comply with the protocol requirements.

4.3.7. Discontinuation of the Study

The study will be discontinued if the Sponsor judges it necessary for any reason.

5. Treatment

5.1. Treatments Administered

This study involves a comparison of a regimen of prasugrel (once-daily 5-mg or 10-mg maintenance dose; or a 30-mg loading dose followed by a once-daily 5-mg or 10-mg maintenance dose) with a regimen of clopidogrel (300-mg loading dose followed by 75-mg maintenance dose or continuation of the once-daily 75-mg maintenance dose for subjects on commercial clopidogrel at randomization) as described in Table TABY.1 (Section 3.1).

The 5-mg prasugrel maintenance dose will be administered to subjects who are at least 75 years of age or have a body weight <60 kg at the time of randomization. The maintenance dose determined at randomization is fixed for the duration of the study, even if the subject's weight or age category subsequently changes. All study treatments are to be administered orally.

Commercial clopidogrel must be discontinued at the time of randomization.

Treatment regimens are described in Table TABY.2 below.

Table TABY.2. Treatment Regimens

Treatment	Dosage Form and Strength	Frequency	Dose Duration
Prasugrel Treatment Group			
Prasugrel loading dose, if required ^a	Three 10-mg tablets and four placebo tablets, matched to clopidogrel	Once	Once
Prasugrel maintenance dose	One 10-mg tablet or one 5-mg tablet and one placebo tablet, matched to clopidogrel	QD	To the end of the study
Clopidogrel Treatment Group			
Clopidogrel loading dose, if required ^a	Four 75-mg tablets and three placebo tablets, matched to prasugrel	Once	Once
Clopidogrel maintenance dose	One 75-mg tablet and one placebo tablet, matched to prasugrel	QD	To the end of the study

Abbreviations: QD = once daily.

^a See Table TABY.1.

The investigator or his/her designee is responsible for explaining the correct use of the investigational agent(s) to the subject and site personnel, verifying that instructions are

followed properly, maintaining accurate records of study drug dispensing and collection, and returning all unused medication to Lilly or its designee at the end of the study.

Subjects should be instructed to contact the investigator as soon as possible if they have a complaint or problem with the study drug so that the situation can be assessed.

5.2. Materials and Supplies

This study incorporates a double-blind, double-dummy design: prasugrel with matching placebo tablets and clopidogrel with matching placebo tablets. Prasugrel drug product is supplied as film-coated 5-mg or 10-mg tablets. Clopidogrel is supplied as film-coated 75 -mg tablets (Plavix® [clopidogrel bisulfate], Sanofi-Synthelabo). Loading doses and maintenance doses are packaged separately. Maintenance doses are packaged in a 1-month supply. A daily maintenance study treatment consists of 2 tablets (1 study drug and 1 placebo).

Clinical study materials will be labeled according to each country's regulatory requirements. All study drug must be stored at 15°C to 30°C (59°F to 86°F).

5.3. Method of Assignment to Treatment

Subjects will be randomly assigned to either prasugrel or clopidogrel through an IVRS with a touch-tone telephone. Randomization will be in a ratio of 1:1. Subjects will be randomized at the country level, and stratified by age and by commercial clopidogrel status (see Table TABY.1 for the stratification by commercial clopidogrel status). In order to balance patient assignment between treatment arms within each stratum, the minimization algorithm introduced by Pocock and Simon (1975) will be implemented within the IVRS system.

5.4. Rationale for Selection of Doses in the Study

5.4.1. Background

Phase 1 and 2 studies evaluated various loading (from 20 mg to 60 mg) and maintenance doses (from 5 mg to 15 mg) of prasugrel. All tested loading and maintenance doses were found to be safe and well tolerated with the exception of the 15-mg MD of prasugrel that was associated with a trend towards increased bleeding events (epistaxis, bruising, or intestinal) compared to the standard regimen of clopidogrel and was discarded for this reason.

Prasugrel was recently evaluated in a completed Phase 3 study, H7T-MC-TAAL (TRITON-TIMI 38). In TRITON-TIMI 38, prasugrel was administered to subjects undergoing PCI; fast and high inhibition of platelet aggregation was warranted in this population. The highest LD of prasugrel (60 mg) was selected because of its faster (as early as 30 minutes) onset of action associated with significantly greater IPA compared to the 300-mg clopidogrel LD. The 10-mg maintenance dose of prasugrel was selected as it

achieved consistent and significantly greater IPA (~30% absolute IPA increase with 5 μ M or 20 μ M ADP) than the 75-mg clopidogrel MD and was found to be safe. The results of TRITON-TIMI 38 showed the superiority of prasugrel over clopidogrel in all pre-specified efficacy endpoints. In both the UA/NSTEMI and All ACS populations, the incidence of the primary composite endpoint of CV death, nonfatal MI, or nonfatal stroke was statistically significantly lower in subjects randomized to prasugrel (LD 60 mg/MD 10 mg) compared to clopidogrel (LD 300 mg/ MD 75 mg). These results supported the hypothesis that greater inhibition of ADP-induced platelet aggregation by a potent oral P2Y₁₂ inhibitor, using the regimen of prasugrel tested, was more effective at preventing ischemic events than standard treatment with clopidogrel. Whereas prasugrel was generally well tolerated, clinical data from TRITON-TIMI 38 suggested that subjects weighing <60 kg and subjects \geq 75 years of age were at increased risk of bleeding after 3 days from the first dose of prasugrel. Maintenance doses of 5 mg are recommended for subjects <60 kg because a reduced MD may reduce bleeding risk in this population who had higher active metabolite exposure. In addition, maintenance doses of 5 mg will be administered for subjects \geq 75 years of age because the vulnerable nature of this population resulted in a higher incidence of bleeding. The trend toward higher active metabolite exposure in subjects \geq 75 years of age in TRITON may have contributed to this increased propensity to bleed. In both subjects weighing <60 kg and subjects \geq 75 years of age, a MD reduction to 5 mg would not be expected to be less efficacious than 75 mg of clopidogrel.

5.4.2. Rationale for Selection of the Loading Dose in TRILOGY ACS

For ACS subjects undergoing PCI, the 60-mg prasugrel LD is warranted to achieve both fast (as early as 30 minutes) and high inhibition of platelet aggregation. However, for subjects who do not undergo PCI (that is, medically managed UA/NSTEMI subjects), a lower prasugrel LD is more appropriate, as higher inhibition of platelet aggregation can be achieved more gradually without initially “over-shooting” the steady state level. A Phase 1 (Jakubowski et al. 2007) study showed that a 30-mg prasugrel LD was well tolerated and achieved IPA levels similar to a 10-mg prasugrel MD within 2 hours. Therefore, a 30-mg prasugrel LD was chosen to be tested in this study.

5.4.3. Rationale for the Selection of the Maintenance Dose in TRILOGY ACS

Consistent with the TRITON-TIMI 38 findings, a 10-mg MD of prasugrel will be administered to all subjects weighing \geq 60 kg and <75 years of age. In order to minimize bleeding, a 5-mg maintenance dose will be administered in subjects weighing <60 kg or \geq 75 years of age. The 5-mg maintenance dose was chosen because it is anticipated, based on pharmacokinetic modeling, that subjects weighing <60 kg and/or \geq 75 years of age who receive a 5-mg MD would have, on average, an exposure to the active

metabolite of prasugrel in the lower range of that observed in heavier and younger subjects receiving the 10-mg MD of prasugrel.

5.5. Timing of Doses

The timing of the first dose of study drug based on commercial clopidogrel status is described in Table TABY.3 below.

Table TABY.3. Timing of First Dose of Study Drug by Commercial Clopidogrel Status

Medically Managed UA/NSTEMI Subjects		
Commercial Clopidogrel Status at Time of Randomization	Randomized Treatment	Timing of First Dose of Study Drug
Stratum 1 Either clopidogrel-naïve or not at steady state ^a on commercial clopidogrel, with a decision for medical management and randomization within 72 hours following the onset of the index event.	<u>Loading Dose/Maintenance Dose:</u> Clopidogrel 300 -mg loading dose followed by 75-mg once-daily maintenance dose <u>or</u> prasugrel 30-mg loading dose followed by 5 /10 -mg once-daily maintenance dose ^b (each administered on a background of low-dose aspirin).	First dose of study drug should be given as soon as possible after randomization and no later than 72 hours following the onset of the index event.
Stratum 2 Commercial clopidogrel loading dose of at least 300 mg administered within 72 hours following the onset of the UA/NSTEMI index event with administration of daily maintenance dose thereafter.	<u>Maintenance Dose Only:</u> Clopidogrel 75-mg once-daily maintenance dose <u>or</u> prasugrel 5/10 -mg once-daily ^b (each administered on a background of low-dose aspirin).	First dose of study drug should be given no later than 24 hours after the last dose of commercial clopidogrel.
Stratum 3 Commercial clopidogrel treatment prior to the index event and subject deemed to be at steady state at the time of the onset of the index event; and MD maintained up until time of randomization.		
^a Subjects defined as clopidogrel-naïve or not at steady state are those subjects who: (i) have not received clopidogrel prior to the index event or have received a maintenance dose of commercial clopidogrel for <5 consecutive days immediately prior to the index event, AND (ii) have NOT received a commercial clopidogrel loading dose within 72 hours following the onset of the index event.		
^b Subjects >75 years of age or <60 kilograms of body weight will receive the 5-mg maintenance dose.		

After the first dose of study drug, subsequent doses should be administered once daily and may be taken with or without food. Subjects should be counseled to take their medication at approximately the same time every day. On days of outpatient clinic visits, subjects who are participating in the platelet function substudy should be counseled to take their medication at least 2 hours prior to the planned visit.

5.6. Blinding

This study incorporates random assignment to study drug in a double-blind, double-dummy manner. To preserve the blinding of the study (detailed in the TRILOGY ACS unblinding plan), only a minimal number of sponsor and CRO personnel who are not associated with the study or its operations will see the randomization table and treatment assignments before the study is complete.

It is expected that the need for unblinding will be extremely uncommon. As all subjects in the study will be on active therapy with a thienopyridine antiplatelet agent (that is, no placebo treatment), every effort will be made to preserve the blind unless there is a compelling reason that knowledge of the specific treatment would alter the medical care of the subject.

Prior to unblinding the treatment assignment of a subject, site personnel should make every effort to contact the CRO Helpline to discuss the clinical circumstances. It is important to note that if an adverse event has occurred, the procedures outlined in Section 6.3.2 of the protocol must be followed in order to document the event.

Emergency unblinding for adverse events may be performed through the IVRS. This option may be used ONLY if the subject's acute well-being requires knowledge of the subject's treatment assignment. Any subject who is unblinded will be permanently discontinued from study drug therapy (see Section 4.3.3), but should be continued in the study.

At a subset of study sites, subjects will also have multiple measurements of platelet function using the Accumetrics VerifyNow® P2Y₁₂ assay. The data output from the device will be encrypted such that the investigator and study coordinator will not have knowledge of the level of platelet inhibition. The encryption code will be held by the CRO with responsibility for data management.

5.7. Concomitant Therapy

All subjects are to be treated with adjunctive aspirin (open-label and commercially available), not to exceed 162 mg, in addition to study drug for the duration of the study. Available data suggest that doses of aspirin higher than 100 mg in association with clopidogrel result in an increased bleeding risk without reduction of risk for ischemic events (Peters et al. 2003). Thus, it is strongly recommended that daily aspirin therapy be administered at an oral dose between 75 and 100 mg. The dose may be increased to a maximum of 325 mg in subjects undergoing PCI, for a period of time as recommended

by the investigator based on the subject's individual clinical circumstances. However, every effort should be made to utilize a lower dose of aspirin.

If the subject experiences an adverse event requiring adjustment of oral antiplatelet therapy and is receiving an oral daily dose of aspirin greater than 81 mg, the investigator should consider reducing the aspirin dose to the range of 75 to 81 mg prior to considering discontinuation of study drug. If the investigator deems further adjustment is needed, alternate aspirin dosing regimens or temporary discontinuation of aspirin is allowable. Changes in aspirin dose regimen must be recorded in the case report form (CRF).

Commercially available aspirin will not be provided by the sponsor. Aspirin will not be considered an investigational drug in this study.

Fibrinolytic therapy administered for ST-segment elevation myocardial infarction, or other indications, after randomization is permitted if the investigator deems it necessary. If fibrinolytic therapy is required, study drug may be temporarily discontinued at the investigator's discretion. If study drug is temporarily discontinued, it should be restarted when, in the investigator's opinion, it is safe to do so.

Oral anticoagulant therapy may be required for atrial fibrillation, deep vein thrombosis, or other indications after the subject is enrolled into the study. In this case, study drug must be temporarily discontinued. Study drug can be restarted when the oral anticoagulant therapy is stopped and the INR is <1.5 ; the investigator should contact the CRO Helpline to determine whether the subject should restart study drug (see Section 4.3.2). If study drug has been temporarily discontinued for >14 days, the investigator should contact the CRO Helpline, who will forward the investigator to the ARO Hotline physician to determine whether the subject should be permanently discontinued from study drug (see Section 4.3.2 and Section 4.3.3).

Based upon the American College of Cardiology/American Heart Association (ACC/AHA) (Anderson et al. 2007) and the European Society of Cardiology (ESC) UA/NSTEMI (Bassand et al. 2007) guidelines regarding discharge management of subjects with ACS, it is recommended that subjects be treated with concomitant long-term therapies according to current guideline recommendations and indication. In particular, subjects with a history of a peptic ulcer should be considered for treatment with proton-pump inhibitors (PPI) or H₂ antagonist at study entry, as prasugrel may increase the risk of GI bleeding in those subjects.

Subjects should discontinue any existing open-label clopidogrel treatment immediately upon randomization. For a list of specifically excluded medications, see the exclusion criteria in Section 4.2 of this document. Open-label maintenance dose of a thienopyridine should not be used after randomization, unless study drug is discontinued. Other cardiac and non-cardiac medications not specifically excluded may be administered at the discretion of the treating physician. Permitted medications include, but are not limited to, histamine 2 receptor (H₂) blockers and proton pump inhibitors (PPIs), oral, sublingual, or intravenous nitrates; calcium channel blockers; beta blockers; angiotensin

converting enzyme inhibitors (ACEIs); angiotensin receptor blockers (ARBs); 3-hydroxy-3-methylglutaryl coenzyme A (HMG Co-A) reductase inhibitors (statins); antiarrhythmic drugs; vasodilators; and intravenous vasopressor agents.

The use of all concomitant medications will be recorded in the CRF.

5.8. Treatment Compliance

Subject compliance with the study drug regimen will be assessed at all visits and upon completing the study. Compliance will be assessed by study drug count. Compliance for each visit interval is defined as taking 80% to 120% of the study drug dosage prescribed for that interval. If a subject is noncompliant, the subject will be counseled by study staff on the importance of taking the prescribed amount of study drug. Subjects will not be discontinued from the study for noncompliance with study drug, as the primary analysis is designated as intent-to-treat (ITT).

6. Efficacy Measures, Health Outcome Measures, and Safety Evaluations

6.1. Efficacy Endpoints

6.1.1. *Primary Efficacy Measure*

The primary efficacy endpoint is the time to the first occurrence of the composite of CV death, MI, or stroke defined as follows.

1) Cardiovascular Death (CV Death):

Death due to documented cardiovascular cause. Additionally, death not clearly attributable to noncardiovascular causes will be considered CV death.

2) Myocardial Infarction (MI):

The definition of MI is adapted from the universal definition of MI (Thygesen et al. 2007) and is dependent on the clinical timing of the event in relation to presenting syndrome and cardiovascular procedures. A subject who experiences any one of the following after randomization will qualify as having had an MI:

- Elevation or re-elevation of the ST segment AND either ischemic chest pain ≥ 20 minutes in duration, or hemodynamic decompensation.
- CK-MB fraction or troponin $> \text{ULN}$, AND either ischemic chest pain (or anginal equivalent) ≥ 20 minutes in duration, or ST-segment deviation ≥ 1 mm in one or more leads. If at the onset of the suspected event, the ischemic biomarker was still elevated as a result of the index event, then there must be demonstration of a falling biomarker level prior to the onset of the suspected event, and the subsequent peak of the ischemic biomarker must be 1.5 times the value prior to the onset of the suspected event. These criteria do not need to be met if the ischemic biomarker is not elevated prior to the onset of the suspected event.
- CK-MB > 3 times ULN on at least 1 sample within 24 hours following PCI (for subjects requiring emergent, urgent, or elective PCI at any time after randomization).
- CK-MB > 5 times ULN on at least 1 sample within 24 hours following CABG (for subjects requiring emergent, urgent, or elective CABG surgery at any time after randomization).
- New Q waves ≥ 0.04 seconds or pathology distinct from that of the index event and thought to be new since randomization.

In order to detect periprocedural MI in subjects undergoing PCI or CABG during the course of the study, it is recommended that 4 blood samples for CK-MB be drawn: 1 prior to the procedure and 3 within the first 24 hours after PCI/CABG. The second sample should be drawn at least 6 hours after PCI. The third sample should be at least 6 hours later (6 to 8 hours recommended), and the fourth sample should be drawn at least 6 hours after the third sample (6 to 8 hours recommended).

In the rare circumstances where CK-MB testing is not available, a troponin >3 times ULN on at least 1 sample within 24 hours following PCI (for subjects requiring emergent, urgent, or elective PCI at any time after randomization) or a troponin >5 times ULN on at least 1 sample within 24 hours following CABG (for subjects requiring emergent, urgent, or elective CABG surgery at any time after randomization) may be used to define and adjudicate a periprocedural MI in place of CK-MBs levels.

3) **Stroke:**

The rapid onset of new, persistent neurologic deficit lasting more than 24 hours. In the case of clinical diagnosis of stroke, computed tomography (CT) or magnetic resonance imaging (MRI) is strongly recommended, but not required. Computed tomography or MRI scans will be considered by the CEC to support the clinical impression. Available supplemental information from head CT or MRI scans will assist in the determination if there is a demonstrable lesion compatible with an acute stroke. Furthermore, all strokes will be classified as either “ischemic” or “hemorrhagic” based on imaging data, if available, or “uncertain cause” if imaging data are not available.

Primary endpoint events must be reported to the sponsor or designee **within 24 hours** after the site staff learns of the clinical event.

All primary endpoints will be adjudicated by the CEC. Study sites should send the required documents that include the relevant completed endpoint CRFs and the requested source documentation to the CEC in a timely fashion for adjudication of the event. Additional details are available in the CEC charter.

6.1.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints are the time to the first occurrence of:

- The composite endpoint of CV death and MI.
- The composite endpoint of CV death, MI, stroke, or rehospitalization for recurrent UA.
- The composite endpoint of all-cause death, MI, or stroke.

- Stent thrombosis.

In addition, the components of the primary and secondary composite endpoints will be analyzed individually in a similar fashion to the primary and secondary composite endpoint (time to first occurrence): CV death, all-cause death, MI, stroke, rehospitalization or for recurrent UA, and any coronary revascularization.

Secondary endpoint events must be reported to the sponsor or designee **within 24 hours** after the site staff learns of the clinical event.

All secondary endpoint events will be adjudicated by the CEC and additional detail regarding endpoint determination can be found in the CEC charter.

6.1.2.1. Rehospitalization for recurrent UA

Rehospitalization for recurrent UA includes chest discomfort or anginal-equivalent symptoms of ≥ 5 minutes duration at rest and at least one of the following:

- ST-segment depression >1 mm in at least two or more ECG leads without elevation of CK-MB, troponin T, or troponin I.
- Performance of an unplanned coronary revascularization procedure (PCI or CABG).

Rehospitalization includes admission to any inpatient unit. Emergency room visits or chest pain unit evaluations lasting for <24 hours are not considered to be rehospitalization. If recurrent UA results in prolongation of a hospitalization initiated for other reasons, it will be considered as a rehospitalization for recurrent UA.

6.1.2.2. Stent thrombosis

Stent thrombosis will be defined based on the Academic Research Consortium definitions (Mauri et al. 2007):

“DEFINITE stent thrombosis

A definite stent thrombosis is considered to have occurred by either angiographic or pathological confirmation.

Angiographic confirmation of stent thrombosis is defined by the presence of an intracoronary thrombus that originates in the stent or in the 5mm proximal or distal to the stent and presence of at least 1 of the following criteria within a 48 hour time window.

- Acute onset of ischemic symptoms at rest
- New ischemic ECG changes that suggest acute ischemia
- Typical rise and fall in cardiac biomarkers

The intracoronary thrombus will be further characterized as being non-occlusive or occlusive as follows:

- Non-occlusive thrombus: intracoronary thrombus is defined as a (spheric, ovoid, or irregular) non-calcified filling defect or lucency surrounded by contrast material (on 3 sides within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization or intraluminal material downstream.
- Occlusive thrombus: TIMI 0 or TIMI 1 intrastent or proximal to stent up to the most adjacent proximal side branch or main branch (if originates from the side branch).

The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion).

Pathological confirmation of stent thrombosis

- Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy

PROBABLE stent thrombosis: clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:

- Any unexplained death within the first 30 days
- Irrespective of the time after the index procedure, any MI that is related to documented ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause.

POSSIBLE stent thrombosis: clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days after intracoronary stenting until end of study follow-up.”

Additional details are available in the CEC charter.

6.1.2.3. Platelet Function Measures

Approximately one-third of the subjects will have platelet function measures performed (N ~3433). At those sites choosing to participate in this substudy, all subjects will have their platelet function measured. Platelet aggregation will be measured by the Accumetrics VerifyNow® P2Y₁₂ and aspirin assays according to the Study Schedule (Attachment TABY.1). The investigators will be trained on the Accumetrics device. If a subject experiences an efficacy endpoint event or a bleeding event, an attempt should be made to obtain an additional blood sample for platelet function measures.

Inhibition of platelet aggregation will be computed by the Accumetrics VerifyNow® P2Y₁₂ assay from 2 measures:

P2Y₁₂ Reaction Units (“PRU”) is an estimate of P2Y₁₂ receptor-mediated platelet aggregation (rate and extent) in response to ADP in the ADP/PGE₁ channel. “BASE” is an independent measurement based on the rate and extent of platelet aggregation in the Thrombin Receptor Activating Peptide (TRAP) channel. The device reported % inhibition is the percent difference between the "PRU" and "BASE" values on any given occasion. The “BASE” value serves as an estimate of the subject’s baseline platelet function independent of P2Y₁₂ receptor inhibition. Percent inhibition, as reported by the Accumetrics VerifyNow P2Y₁₂ device, is calculated from PRU and BASE values as follows:

$$\% \text{ Inhibition} = (1 - \text{PRU}/\text{Base}) \times 100$$

Subject response to aspirin will be measured in aspirin reaction units (ARU) using the VerifyNow ASA cartridge.

6.1.2.3.1. Other Biomarkers

Blood samples for an additional exploratory analysis will be collected as core laboratory measurements, as described below and in the Study Schedule (Attachment TABY.1). Biomarkers of inflammation (high-sensitivity C-reactive protein [hsCRP]) and hemodynamic stress (N-terminal prohormone brain natriuretic peptide [NT-proBNP] or brain natriuretic peptide [BNP]) will be obtained to explore their value as prognostic indicators of risk and response to therapy.

6.1.2.3.2. Stored Samples

Blood samples for directed genomic testing will be collected at Visit 1. DNA derived from these samples will be used to determine the influence of genetic variants on treatment response, metabolism, action, or adverse events. These evaluations may include genetic analysis of drug transporter, metabolizing enzymes such as CYP450, and/or P2Y₁₂ receptor polymorphisms. These samples will retain the subject identifier and, therefore, will not be stored indefinitely, but will be destroyed within 3 years after the last subject visit for the study.

6.1.3. Sample Banking

Sample banking is an optional part of this study. DNA banked samples will be anonymized and stored. DNA from banked samples may be used to further explore genetic relationships between disease susceptibility, disease outcomes, and drug responses.

Detailed information regarding sample banking will be described in a separate protocol addendum and subject consent will be obtained separately.

6.2. Health Outcome Measures

Healthcare resource use will be collected in the CRF from the time of enrollment to end of follow-up for all subjects in the study. Measures of resource use will include all-cause hospitalizations and associated lengths of stay (intensive care and routine), emergency room visits, major procedures (such as catheterization, percutaneous intervention, bypass surgery), and admissions to non-acute care facilities. Cumulative healthcare costs for the duration of the study will be estimated for subjects in the United States using hospital billing data.

Quality of life will be measured in all subjects at baseline using the EQ-5D (except at a small minority of sites where an appropriate translation of the questionnaire is unavailable) and with additional selected measures in a subgroup of subjects. The data will be completed following informed consent and prior to randomization/treatment.

If prasugrel is found to be more effective and more costly than clopidogrel, the long term cost effectiveness of prasugrel (incremental cost per quality-adjusted life-year gained) will be examined.

Additional details of health outcome measures are provided in Attachment TABY.3.

6.3. Safety Evaluations

Investigators are responsible for monitoring the safety of subjects who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject.

The investigator is responsible for appropriate medical care of subjects during the study.

The investigator remains responsible for following, through an appropriate healthcare option, adverse events that are serious or that cause the subject to discontinue study drug before completing the study. The subject should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

Safety evaluations will be performed by recording clinical adverse events and by monitoring laboratory values.

6.3.1. Safety Endpoints

6.3.1.1. Bleeding events

Safety endpoints include the following bleeding events classified according to the TIMI criteria (Bovill et al. 1991) and GUSTO definitions (GUSTO Investigators 1993):

- **Non-CABG-related TIMI major bleeding** is any ICH **OR** any clinically overt bleeding (including bleeding evident on imaging studies) associated with a fall in hemoglobin (Hgb) of ≥ 5 gm/dL from baseline (accounting for the effect of transfusions on change in Hgb, defined as 1 unit packed red blood cells [RBCs] = 1 gm/dL Hgb = 3% hematocrit [Hct]).
- **Non-CABG-related TIMI life-threatening bleeding** is any non-CABG-related TIMI major bleeding that is fatal, leads to hypotension that requires treatment with intravenous vasopressor agents, **OR** requires surgical intervention for ongoing bleeding, **OR** necessitates the transfusion of 4 or more units of blood (whole blood or packed RBCs) over a 48-hour period, **OR** any symptomatic ICH.
- **Non-CABG-related TIMI minor bleeding** is any clinically overt bleeding (including bleeding evident on imaging studies) associated with a fall in Hgb of ≥ 3 gm/dL, but < 5 gm/dL from baseline (accounting for the effect of transfusions on change in Hgb, defined as 1 unit packed RBCs = 1 gm/dL Hgb = 3% Hct).
- **Non-CABG-related TIMI minimal bleeding** is any clinically overt bleeding (including bleeding evident on imaging studies) associated with a fall in Hgb of < 3 gm/dL from baseline (accounting for the effect of transfusions on change in Hgb, defined as 1 unit packed RBCs = 1 gm/dL Hgb = 3% Hct).
- **Non-CABG-related GUSTO severe or life-threatening bleeding** is any ICH **OR** any bleeding event resulting in substantial hemodynamic compromise requiring treatment.
- **Non-CABG-related GUSTO moderate bleeding** is any bleeding event resulting in the need for transfusion that is not considered a GUSTO severe or life-threatening bleed.
- **Non-CABG-related GUSTO mild bleeding** is any other bleeding event that does not require transfusion or cause hemodynamic compromise.

Additional safety endpoints include the following:

- Incidence of fatal bleeding or ICH.
- Incidence of CABG-related bleeding events.

Bleeding events will be analyzed by type of bleeding event (that is, fatal, life-threatening, ICH, requiring transfusion, etc.) and by the use of bleeding classification scales (that is, the TIMI classification or the GUSTO classification). Use of a combination of bleeding scales and need for transfusion has been recently recommended for clinical studies in subjects with acute coronary syndromes (ACS) (Rao et al. 2006).

Bleeding endpoints must be reported to the sponsor or designee **within 24 hours** after the site staff learns of the safety event. TIMI bleeding events will be adjudicated by the CEC. Additional details are available in the CEC charter.

6.3.2. Adverse Events

The standard for reporting adverse events will be that which meets the most stringent requirements among the regulatory agencies of the countries participating in this study. For purposes of collecting and evaluating all information about Lilly drugs used in clinical studies, a clinical study adverse event is any untoward medical occurrence in a subject administered a pharmaceutical product, without regard to the possibility of a causal relationship.

Cases of pregnancy should be reported for tracking purposes. Additional data on pregnancy, fetal outcome, and breastfeeding are collected and entered into the safety database for regulatory reporting and drug safety evaluation. These data also include cases of pregnancies that occur during paternal exposures to Lilly study drug.

Individual clinical events likely due to lack of drug effect cannot be considered related to study drug in a clinical study.

Prior to enrollment, study site personnel will note the occurrence and nature of each subject's medical condition(s) in the appropriate section of the CRF. During the study, site personnel will again note any change in the condition(s) and the occurrence and nature of any adverse events.

After the informed consent document is signed, all adverse events related to protocol procedures are reported to Lilly or its designee.

All adverse events occurring after the subject receives the first dose of study drug must be reported to Lilly or its designee by recording the event in the adverse event section of the CRF.

The investigator will be instructed to record his or her assessment of the potential relatedness of each adverse event to study drug.

In addition, study site personnel must report to Lilly or its designee within 24 hours, any **serious** adverse event or any instance where the investigator **unblinds** a subject's treatment group assignment for any other reason (see Section 5.6).

If a subject's study drug treatment is discontinued as a result of an adverse event, study site personnel must clearly document the circumstances and data leading to any such discontinuation of treatment, using the CRF (see Section 4.3).

Subjects who permanently discontinue study drug prior to completing the study should have an on-site visit performed and will remain in the study to be evaluated for efficacy and safety endpoints. Adverse events, serious and non serious, will be collected for 30 days after the last dose of study drug. Thereafter, serious adverse events will not be reported unless the investigator feels the events were related to either study drug or a protocol procedure.

In cases where the investigator notices an unanticipated benefit to the subject, study site personnel should enter "unexpected benefit" with the actual event term (for example, the complete actual term would be "unexpected benefit—sleeping longer").

6.3.2.1. Serious Adverse Events

Serious adverse event (SAE) collection begins after the subject has signed informed consent and has received study drug. If a subject experiences a SAE after signing informed consent, but prior to receiving study drug, the event will NOT be collected unless the investigator feels the event may have been caused by a protocol procedure.

A serious adverse event is any clinical event that results in:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- an event that is considered significant by the investigator for any other reason.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

In this study, events leading to the clinical outcomes of death, MI, stroke, stent thrombosis, or rehospitalization for recurrent UA will be included as part of the efficacy analysis for this study and will not be recorded as SAEs unless the investigator believes the event may have been caused by the study drug. All relevant medical information will be collected on the eCRF to satisfy SAE reporting requirements so that if an investigator-reported endpoint is subsequently not adjudicated by the CEC as an endpoint and the

event meets serious criteria, the CEC will notify the contract research organization (CRO) of this finding within 24 hours following the adjudication decision.

All other SAEs and study endpoints must be reported to the CRO **within 24 hours** after the site staff learns of the clinical event.

The CRO will be alerted to SAEs occurring within 30 days of a subject's discontinuation, regardless of the investigator's opinion of causation. Thereafter, SAEs are not required to be reported unless the investigator feels the events were related to either study drug or a protocol procedure.

6.3.2.2. Non-benign Neoplasm

A cancer surveillance plan will be implemented. It will include prospective data collection of selected risk factors for malignancy, history of malignancy, selected cancer screening tests, signs and symptoms suggestive of malignancy, and suspected new or recurrent malignancies during the study. Suspected malignancy events will be adjudicated by a specific Clinical Endpoint Committee. Additional details are available in the CEC charter dedicated to non-benign neoplasms.

6.3.3. Other Safety

Standard safety laboratory tests, including chemistry and hematology panels, will be performed at the times specified in the Study Schedule (Attachment TABY.1). A urine or serum pregnancy test (for females of childbearing potential) will be performed at the study site or at a local laboratory. Chemistry and hematology laboratory tests (Attachment TABY.2) will be analyzed by a central laboratory. The study site will be contacted by the central laboratory for values regarded as alarming (as determined by the sponsor or its designee). Laboratory tests deemed necessary by the investigator for subject care should be analyzed in a local laboratory.

Investigators must document their review of each laboratory report. In addition, the investigator must determine if the result of the laboratory test is considered an adverse event or SAE and perform clinical follow-up and/or SAE reporting as necessary and follow the subject's event until resolution. If the investigator requires consultation, the CRO Helpline should be contacted.

Samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

Routine 12-lead ECGs will be obtained according to the Study Schedule (see Attachment TABY.1). Electrocardiograms will be recorded and stored at the site and evaluated by the investigator. Investigators must document their review of each study-specific ECG by signing or initialing and dating each report.

6.3.4. Safety Monitoring

The Lilly clinical research physician and the CRO will monitor safety data throughout the course of the study. The CRO will be responsible for safety monitoring follow-up at the site throughout the course of the study. The Lilly Global Patient Safety physician and the CRO will review trends in laboratory analyses and SAEs at periodic intervals.

For the purposes of this study in which mortality is an endpoint, all SAE reports and primary, secondary, and safety endpoints, including events with a fatal outcome, will be reviewed during the clinical study in a blinded manner by the Study Operations Committee.

Clinical endpoints, bleeding endpoints, and SAEs will be reviewed regularly for safety and efficacy by an external independent Data Monitoring Committee (DMC). The DMC will be presented with data that are blinded at the group level (Treatment A versus Treatment B). If necessary for safety concerns, completely unblinded data will be provided to the DMC by the designated unblinded data analysis group at the CRO. The DMC will operate under a written charter that includes well-defined standard operating procedures.

Lilly Global Patient Safety and the CRO will review SAEs within timeframes mandated by company procedures. Unblinding of individual death or clinical adverse events deemed serious will be conducted by Lilly Global Patient Safety and the CRO in order to comply with regulatory reporting and safety monitoring requirements. These measures will preserve the integrity of the data collected during this study and minimize any potential for bias while providing for appropriate safety monitoring.

If safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, only the DMC can conduct additional analyses of the safety data.

6.3.5. Complaint Handling

Lilly collects product complaints on study drugs and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Complaints related to unblinded comparator drugs or concomitant drugs/drug delivery systems are reported directly to the manufacturers of those drugs/devices in accordance with the package insert.

For blinded studies, all product complaints associated with material packaged, labeled, and released by Lilly will be reported via product complaint forms.

The investigator or his/her designee is responsible for handling the following aspects of the complaint process in accordance with the instructions provided for this study:

- Recording a complete description of the product complaint reported and any associated adverse events using the study-specific complaint forms provided for this purpose.
- Faxing the completed product complaint form within 24 hours to Lilly or its designee.
- Determining when a drug is to be returned for investigation.

6.4. Appropriateness of Measurements

All safety and efficacy measures are widely used and generally regarded as reliable, accurate, and relevant in studies of subjects with UA/NSTEMI.

7. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- Provide instructional material to the study sites, as appropriate.
- Sponsor a start-up training session to instruct the investigators and study coordinators (this session will give instruction on the protocol, the completion of the CRFs, and study procedures).
- Make periodic visits to the study site.
- Be available for consultation and stay in contact with the study site personnel via e-mail, mail, telephone, and/or fax.
- Review and evaluate CRF data and use standard computer edits to detect errors in data collection.
- Conduct a quality review of the database.
- Verify the quality of the data.

In addition, Lilly or its representatives may periodically check a sample of the subject data recorded against source documents at the study site. The study may be audited by Lilly Medical Quality Assurance (MQA) or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

To ensure the safety of participants in the study and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and subject medical records in the subject files as original source documents for the study. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

7.1. Data Entry and Computerized Systems

Case report form data collected by the CRO will be encoded by the CRO and stored electronically in the CRO's database system. Validated data will subsequently be transferred to the sponsor's data warehouse using standard MVS (that is, a mainframe IBM computer to which data are transferred) host file transfer processes.

Central laboratory data will be stored electronically in the central laboratory's database system. Data will subsequently be transferred from the contract laboratory to the CRO database for data validation and analysis. The CRO will then transfer the central lab data to the sponsor, along with the CRF data as described above.

Any data for which the CRF will serve as the source document will be identified and documented by each site in that site's study file.

8. Sample Size and Statistical Methods

8.1. Determination of Sample Size

Sample size calculations were done to achieve 90% power for those subjects <75 years of age. To detect a 22% relative risk reduction with prasugrel versus clopidogrel, using a two-sided test at $\alpha = 0.05$, a total of 688 subjects experiencing an event of the composite primary endpoint is required. The following additional assumptions were used to determine the required sample size for the study:

- Eight percent (8%) clopidogrel event rate for the primary endpoint the first year followed by 4% event rate the second year (Fox et al. 2004; Chan et al. 2007; Morrow et al 2007).
- Five percent (5%) annual drop-out rate (that is, lost to follow-up or revoked consent).
- Minimum follow-up of 6 months on all subjects <75 years old.

Under these assumptions, approximately 7800 subjects <75 years old will need to be randomized to obtain the required number of events over a projected accrual period of approximately 24 months with a maximum follow-up period of up to 30 months. This will result in an approximate 18-month median follow-up time.

Since this study will be endpoint-driven, the actual number of subjects enrolled may vary, depending on the observed event rates. Termination of the study will be triggered by a projection that 688 subjects will experience an event of the composite triple endpoint, and all subjects less than 75 years of age will either complete at least 6 months of follow-up or discontinue before 6 months of follow-up. Thus, instead of continuing enrollment in subjects less than 75 years of age until the actual number of events (688) have occurred, enrollment will continue until the sponsor has projected that 688 events will occur. This determination will be made by the sponsor in conjunction with the Executive Committee. The projected number of events will be based on the observed event rate (pooled over both treatment groups since treatment assignment will still be blinded) and the recruitment rate.

Enrollment of the elderly will continue until at least 2000 subjects ≥ 75 years of age have been randomized into the study, with the last subject having either completed at least 3 months of follow-up (completion of Visit 4 per study schedule) or discontinued before 3 months of follow-up. However, enrollment in the cohort of subjects 75 years of age or greater (elderly) will be stopped when a maximum of 2500 subjects have been enrolled.

8.2. Statistical and Analytical Plans

8.2.1. General Considerations

Primary analyses will be conducted on CEC-adjudicated endpoints. Specific definitions of efficacy and safety endpoints are included in the protocol as well as the CEC charter. In the composite endpoint analyses, reaching any component of the composite endpoint will be considered as reaching the composite endpoint. In analyzing non-composite endpoints, reaching only the specific endpoint will be considered (whether or not it is the first event to occur).

Two key datasets are of interest: the intent-to-treat (ITT) set consisting of all randomized subjects and the treated set consisting of subjects receiving at least 1 dose of study drug (including the loading dose). Efficacy endpoint analyses will be carried out using the ITT set.

Safety endpoint analyses will be carried out using the treated set. The focus of the safety analyses is any safety event (including bleeding event, other treatment-emergent adverse event, or abnormal laboratory value) that occurred in a treated subject while “at risk.” A subject will be classified as “treated” if they receive at least one dose of study drug, either a loading dose or maintenance dose. A subject will be considered “at risk” during the period from the administration of the first dose of study drug up through 7 days after permanent study drug discontinuation, or the subject’s discontinuation visit, whichever is earlier. If an adverse event is classified by the investigator as “study drug related”, it will be considered part of the “at risk” set, regardless of the timing.

All analyses will be carried out for the subjects <75 years of age, all subjects, and subjects ≥ 75 years of age.

Time-to-event is defined as the time from randomization to the onset of the endpoint. Comparison of the treatment groups relative to primary and secondary efficacy endpoints will be carried out using time-to-first event analysis via a stratified two-sided log-rank test. The stratification variable consists of 3 levels as given in (Table TABY.1) within both the subjects <75 years of age and subjects ≥ 75 years of age. This stratification is being performed so that any possible bias related to switching subjects with prior commercial clopidogrel exposure to prasugrel may be evaluated. Available information on the vital status of subjects lost to follow-up or who withdrew consent will be included in the analyses of the all-cause death endpoint.

The potential influence of baseline risk factors, additively or interactively, will be assessed in an exploratory manner using the Cox proportional hazards model. Comparison of the proportions of events will be carried out using Pearson’s uncorrected chi-square test of homogeneity.

For various outcomes, confidence intervals for hazard ratios (under the assumption of proportional hazards) will be provided. All confidence intervals will be two-sided with a

95% confidence level, and all hypothesis tests will be two-sided carried out at a significance level of 0.05.

Detailed instructions for the statistical analyses will be outlined in a separate statistical analysis plan. Development and implementation of this document will be the responsibility of Lilly or their designee. All statistical analyses of this study will be performed under the guidance and approval of a statistician at Lilly, but may be performed at a CRO. Analysis data sets will be reviewed by an independent statistician at the ARO and archived at Lilly, Indianapolis, Indiana, USA. To comply with publication requirements, the analysis of the primary endpoint will be replicated by the ARO as an independent verification of the primary endpoint results.

8.2.2. Subject Disposition

Final subject disposition and reasons for study discontinuation will be summarized by treatment group. The percent of subjects discontinuing study drug treatment, withdrawing from the study from each treatment group, and lost to follow-up will be compared using Pearson's chi-square test of homogeneity.

8.2.3. Subject Characteristics

Subject characteristics such as clinical presentation, sex, age, geographic region, ethnicity, number of high-risk features, and medical history will be obtained at baseline and will be summarized by treatment group. The summaries will include descriptive statistics (sample size, mean, standard deviation, minimum, median, and maximum) for the continuous variables and frequencies and percentages for the categorical variables. Subject characteristics on a continuous scale at baseline will be compared using analysis of variance (ANOVA) methodology. Subject characteristics on a categorical scale at baseline will be compared using Pearson's chi-square test of homogeneity.

8.2.4. Concomitant Therapy

The effect of concomitant medications on the primary efficacy endpoint will be assessed by conducting subgroup analyses on certain medication classes. In addition, a Cox proportional hazard model will be carried out with treatment, subgroup, and the interaction term in the model. Analyses will include, but not be limited to, the effect of HMG Co-A reductase inhibitors (statins), ACEI, beta blockers, ARB, GPIIB/IIIA, and the dose of aspirin. Corresponding two-tailed 95% confidence intervals for the hazard ratios will be provided. In addition, prior and concomitant medications will be summarized by treatment group.

8.2.5. Treatment Compliance

Treatment compliance will be defined by the following treatment compliance ratio: the number of maintenance doses taken by the subject divided by the number of drug doses

prescribed for that interval. Compliance is defined as taking from 80% to 120% of the study drug dosage prescribed. Rates of compliance will be compared between treatment groups using Pearson's chi-square test.

8.2.6. Primary Outcome and Methodology

The primary endpoint is the composite of CV death, MI, or stroke. Time from randomization to the first occurrence of the primary endpoint (CV death, MI, or stroke, whichever occurs first) will be compared between treatment groups using a stratified two-sided log-rank test where the strata are subject category as defined in Table TABY.1. Corresponding survival curves will be estimated by the Kaplan-Meier method and two-sided 95% confidence intervals for the average hazard ratio will be provided with the use of the Cox proportional hazards model.

Primary analyses will be carried out in a hierarchical manner. At the first step, treatment groups will be compared within the <75 year old subjects using methodology above. Conditional on successfully establishing superiority of prasugrel over clopidogrel in the <75 year old subjects, treatment groups will be compared on all subjects using a stratified two-sided log-rank test with two stratification variables: subject category as in Table TABY.1 and age (<75 or ≥ 75).

8.2.7. Efficacy Analyses – Secondary Endpoints

The three secondary composite endpoints, stent thrombosis, and individual event endpoints will be tested at $\alpha = 0.05$ (two-sided) in patients < 75 years of age using the same methodology as the primary outcome, that is, a stratified log-rank test for time to first occurrence. Individual endpoints include all cause death, CV death, MI (fatal and nonfatal), stroke (fatal and nonfatal), rehospitalization for recurrent UA, and any coronary revascularization. In addition, those events that contribute to the primary composite outcome will be broken down into mutually exclusive components (CV death, nonfatal MI, nonfatal stroke) with percentages given for each treatment group and compared between treatment groups with a Cochran-Mantel-Haenszel chi-square stratified by subject category.

In addition, analyses will be conducted on the three secondary composite endpoints, stent thrombosis, and individual event endpoints for all subjects and within subjects ≥ 75 years of age. Due to the small sample size of the very elderly population (2000-2500), there may not be adequate statistical power to make a meaningful conclusion on this cohort.

The following analyses will be conducted in a subset of study subjects using platelet aggregation (PA) as measured by the Accumetrics VerifyNow® P2Y₁₂ assay. Baseline demographic and medical history will be compared between those subject included in the PA analysis and those not included in the analysis. Analyses will be done in the <75 year old subjects, all subjects and the greater than 75 year old subjects.

- To test the hypothesis that a lower risk of the composite endpoint will be seen for those subjects with lower levels of PA, a Cox regression model will be performed with PA level as a time-dependent covariate in the model. In addition, the stratification variable of subject category (as in Table TABY.1) will be included in the model. When analyzing all subjects, the additional strata variable of age (<75 versus ≥75) will also be included. Platelet aggregation will be used as a continuous measure in the model. Additional models will evaluate covariates (in addition to PA) such as treatment group, gender, comorbid conditions, etc. A Cox regression will also be conducted using the 2-hour post-loading dose PA measurement in the model to test whether a PA measurement obtained shortly after randomization is predictive of subsequent event-free survival. In addition, the PA will be analyzed by quartiles, that is, the data will be divided into 4 equal groups (based on last available PA measurement prior to event) with event rates compared between quartiles. Similar analyses as described for composite endpoint will be done for bleeding outcomes, that is, TIMI major bleeds, TIMI major and/or minor bleeds, etc.
- Platelet aggregation (PA) measured at 2 hours, 30 days, and most recently prior to censoring will be compared between treatment groups using separate ANOVAs with treatment, the stratification variable, and baseline PA in the model. In addition, the mean PA will be compared between treatment groups across the entire maintenance phase of the study within a likelihood-based mixed-effects model repeated measures analysis. This approach accounts for the bias caused by non-random missing data better than imputing missing values using a last observation carried forward approach. When analyzing all subjects, the additional stratification variable of age will be included.
- The mixed-effects model repeated measures analysis of the platelet aggregation measurements from the Accumetrics VerifyNow® P2Y₁₂ assay across maintenance dose visits (30 days and subsequent measures) will be utilized to estimate intrasubject and intersubject variability for prasugrel and clopidogrel. Intrasubject and intersubject variability will be compared between the prasugrel and clopidogrel treatment groups.
- For those subjects who entered the study on clopidogrel, a Cox regression will be done for the primary composite outcome with randomized treatment, baseline PA (measured prior to receiving first dose of study drug), and the interaction between baseline PA and randomized treatment. The interaction test will test the hypothesis that the difference between treatment groups is dependent on the PA produced by clopidogrel. For example, if a subject achieves a low level of PA on clopidogrel prior to randomization, the difference in survival between treatment groups would be smaller than for those subjects who have a high level of PA on clopidogrel prior to randomization. It is hypothesized that for the latter subjects, the difference between treatment groups would be the greatest.

- To assess treatment interaction in subjects with genetic variation on platelet function, analysis of variance model will be used with PA as the dependent variable; and strata, treatment, genetic variation (yes/no), and the interaction between treatment and genetic variation will be done. If the interaction is significant, then tests will be done within each treatment group to assess whether there is a difference between subjects with and without a genetic variation. Additional models may be explored with other covariates. Similarly, to assess the treatment interaction with genetic variation on clinical outcomes, a Cox proportional hazard model will be done for time to first occurrence of clinical outcome with strata, treatment, genetic variation, and the interaction between treatment and genetic variation. When analyzing all subjects, both strata (subject category and age) will be included.

8.2.8. Health Outcome Analyses

The prospective economic and quality-of-life portion of the study will be conducted to detect differences between treatment groups in medical resource use, cost, and health-related quality of life. The DCRI will be responsible for collecting, analyzing, and reporting these data, as well as preparing abstracts and manuscripts. DCRI will work closely with the Health Outcomes group at Lilly and Daiichi Sankyo.

The analysis will involve a comparison between treatment groups of medical care resource use, cost, and health-related quality of life for the period of follow-up in the study. The primary analyses will be restricted to subjects enrolled in the United States (U.S.). In sensitivity analyses, overall resource use patterns in the study will be quantified by attaching U.S. cost weights to resource use variables for all subjects in the study. Country-specific economic analyses will be performed as needed by local experts.

In addition to assessing the effect of treatment on cost and quality of life, the influence of levels of platelet aggregation on resource use, cost, and cost effectiveness will be explored. If prasugrel is found to increase both effectiveness and cost, a long-term cost-effectiveness analysis that assesses the incremental cost of prasugrel per quality-adjusted life-year gained will be performed. Additional details of the planned analyses are provided in Attachment TABY.3.

8.2.9. Safety Analyses

8.2.9.1. Safety Endpoint Analyses

Time to first occurrence of TIMI and GUSTO defined bleeds (as in Section 2.2.2) will be compared between treatment groups with stratified log-rank test. Corresponding 95% confidence interval for the hazard ratio of prasugrel versus clopidogrel will be constructed. The primary analysis of bleeding events will be for those events occurring during the “at risk” time period as defined in Section 8.2.1. A secondary analysis will consist of all events, regardless of their timing. Analyses of bleeds and other safety

outcomes will be done for <75 year old subjects, all subjects, and the ≥ 75 year old subjects alone.

In addition, 95% confidence intervals for the relative risk of prasugrel versus clopidogrel will be constructed for the occurrence of the additional safety measures listed in Section 6.3.1 (for example, fatal bleeding, ICH, etc.).

8.2.9.2. Adverse Event and Laboratory Analyses

Adverse events will be summarized as treatment-emergent adverse events (TEAEs). Treatment-emergent adverse events are defined as events that first occurred or worsened after baseline. Rates of TEAEs occurring during the “at risk” period (see Section 8.2.1) will be presented for each treatment group and between-group comparisons will be performed using a chi-square test. A secondary sensitivity analysis will also be done that includes all adverse events regardless of timing. Serious adverse events (SAEs) will be compared in a similar fashion.

Change from baseline to safety endpoint (last available observation) will be compared between treatment groups for laboratory measurements (for example, chemistry and hematology measures) using an ANOVA with treatment and prior clopidogrel use in the statistical model. The incidence of treatment-emergent abnormal laboratory values (defined as a change from normal at baseline to abnormal at endpoint) will be tabulated by treatment group and compared between groups using a chi-square test.

8.2.10. Subgroup Analyses for Efficacy and Safety

Subgroup analyses, relative to primary and secondary efficacy endpoints and key safety endpoints will include, but will not be limited to, treatment group comparisons within subject characteristics (for example, age, sex, weight, ethnicity, medical history), baseline risk including prior treatment with clopidogrel (subject category as in Table TABY.1), all subjects receiving 5 mg dose, co-morbid conditions, and concomitant medications, use of GPIIb/IIIa, and geographic region as outlined in the statistical analysis plan. Primary efficacy and safety analysis will also be summarized by country. In addition, endpoints will be evaluated according to each of the enrichment criteria listed in Inclusion Criterion #3 in Section 4.1 (age ≥ 60 years; Prior MI evidenced by pre-existing Q waves, or demonstration of infarction on imaging studies, or prior documentation of elevated cardiac markers; Diabetes Mellitus - defined by concomitant treatment with an oral hypoglycemic agent and/or insulin; and prior PCI/CABG). Treatment-by-subgroup interaction tests will be carried out to determine whether treatment differences are similar for each subgroup category. Hazard ratios will be calculated for the three strata separately for the primary efficacy and safety outcomes to evaluate whether there is a consistent effect.

8.2.11. Interim Analyses

Periodic interim analyses will be conducted under the auspices of an independent, external DMC assigned to this study. The DMC will be presented with data that are blinded at the group level (Treatment A versus Treatment B). If necessary for safety concerns, completely unblinded data will be provided to the DMC by the designated unblinded data analysis group at the CRO. Only the DMC is authorized to evaluate unblinded interim efficacy and safety analyses. Study sites will receive information about interim results ONLY if they need to know for the safety of their subjects.

Interim analyses, including a review of safety and efficacy data, will be conducted by the DMC approximately every 6 months, starting 28 March 2009. Further details will be included in the DMC Charter. At all interim analyses, consideration will be given to termination of the study if the data suggest a strong likelihood of excessive life-threatening bleeding or deaths in the prasugrel group compared with the clopidogrel group. There will be no consideration for stopping early due to efficacy, and therefore no adjustment to final alpha level for efficacy testing will be made.

Recommendations by the DMC to terminate the study early due to safety concerns will be guided by the algorithms provided in the DMC charter. However, the DMC has the authority to recommend stopping the study or continuing the study based on their clinical interpretation and the risk/benefit profile of the data that they are reviewing. Final decisions concerning study conduct will rest with the sponsor, in consultation with the ARO.

8.2.11.1. Frequency and Objectives of Interim Reports

Tabular summaries (blinded at the group level, or unblinded if deemed necessary by the DMC) of deaths, MIs, strokes, life-threatening bleeding, non-CABG-related TIMI major bleeding, selected potentially clinically significant laboratory values (from the central laboratory), serious adverse events, and other relevant safety information will be sent to the DMC by the independent Data Analysis Group (DAG). These summaries will be presented to the DMC for the <75 years of age cohort, the ≥75 years of age cohort, and the all patients cohort. The independent DAG and statistician are independent of the Sponsors, the ARO, and the CRO.

8.2.11.2. Early Termination due to Excessive Life Threatening Bleeding or Deaths

At all interim analyses, consideration will be given to termination of the study if the accumulating data suggest a strong likelihood of excessive TIMI life-threatening bleeding. TIMI life-threatening bleeding rates in the prasugrel group will be considered excessive if the hazard ratio is >2.0 with a p-value <0.001.

At all interim assessments, consideration will be given to termination of the study if the accumulating data suggest a strong likelihood of an excessive number of deaths. The number of deaths in the prasugrel group will be considered excessive if the lower bound

of a 99% confidence interval for the difference in proportions of deaths, prasugrel versus clopidogrel, excludes 0.

9. Informed Consent, Ethical Review, and Regulatory Considerations

9.1. Informed Consent

The investigator is responsible for ensuring that the subject understands the risks and benefits of participating in the study, including answering any questions the subject may have throughout the study and sharing in a timely manner any new information that may be relevant to the subject's willingness to continue his or her participation in the study.

The informed consent document (ICD) will be used to explain the risks and benefits of study participation to the subject in simple terms before the subject is entered into the study, and to document that the subject is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study.

The investigator is responsible for ensuring that written informed consent is given by each subject or legal representative. This includes obtaining the appropriate signatures and dates on the ICD prior to the performance of any protocol procedures and prior to the administration of study drug.

As used in this protocol, the term "informed consent" includes all consent and assent given by subjects or their legal representatives.

9.2. Ethical Review

Lilly must agree with all ICDs before they are submitted to the ERB and are used at study sites. All ICDs must be compliant with the International Conference on Harmonization guideline on GCP. Informed consent obtained under special circumstances may occur only if allowed by local laws and regulations, and performed in accordance with a written process approved by Lilly.

The investigator will provide Lilly with documentation of ERB approval of the protocol and the informed consent document *before* the study may begin at the study sites. Any member of the ERB who is directly affiliated with this study as an investigator or as site personnel must abstain from the ERB's vote on the approval of the protocol. The ERBs will review the protocol as required.

The investigator will supply the following to the study site's ERB(s):

- the study protocol
- the current Investigator's Brochure or package labeling and updates during the course of the study
- informed consent document
- relevant curricula vitae.

9.3. Regulatory Considerations

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCP and the applicable laws and regulations. The investigator, head of the medical institution, or designee, will promptly submit the protocol to the applicable ERB(s).

Prasugrel is being studied in the United States under a United States Investigational New Drug (IND) application. The US IND number is 63,449.

All or some of the obligations of the sponsor will be assigned to a CRO or an ARO.

An identification code assigned by the interactive voice response system (IVRS) to each subject will be used in lieu of the subject's name to protect the subject's identity when reporting adverse events and/or other study-related data.

9.3.1. Investigator Information

Qualified physicians including, but not limited to, those with a specialty in cardiology will participate as investigators in this clinical study.

9.3.2. Protocol Signatures

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative or designee.

9.3.3. Final Report Signature

The clinical study report coordinating investigator and the sponsor's responsible medical officer will sign the final clinical study report for this study, each confirming that to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

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Protocol Attachment TABY.1. Study Schedule

Study Schedule for Study H7T-MC-TABY (TRILOGY ACS)

	Screen	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visits 6, 8, 10, 12	Visits 7, 9, 11		Visit 13 / Final Visit
Procedure		Day 1 ^a	<u>Telephone Contact</u> Day 14 (±3 days)	Day 30 (±3 days)	Month 3 (±7 days)	Month 6 (±14 days)	<u>Telephone Contacts</u> Months 9, 15, 21, and 27 (±14 days)	Months 12, 18, and 24 (±14 days)	Early Disc. From Study Drug ^b	Month 30 / Disc. From Study
Screening, review all available data (medical history, physical exam, ECG, pre-existing conditions, Creatinine, Troponin I/T or CK-MB) to determine eligibility for study	•									
Informed consent (prior to study procedures)		•								
Randomization through IVRS		•								
Directed physical exam ^o		•		•	•	•		•	•	•
Vital signs		•		•	•	•		•	•	•
ECG		•		•		•		• ^m	•	•

	Screen	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visits 6, 8, 10, 12	Visits 7, 9, 11		Visit 13 / Final Visit
Procedure		Day 1 ^a	<u>Telephone Contact</u> Day 14 (±3 days)	Day 30 (±3 days)	Month 3 (±7 days)	Month 6 (±14 days)	<u>Telephone Contacts</u> Months 9, 15, 21, and 27 (±14 days)	Months 12, 18, and 24 (±14 days)	Early Disc. From Study Drug ^b	Month 30 / Disc. From Study
Concomitant medications recorded (including aspirin dose) ^c		•	•	•	•	•	•	•	•	•
Adverse events recorded		•	•	•	•	•	•	•	•	•
Study Drug										
First dosed ^d		•								
Study drug MD dispensed ^e		•		•	•	•		•		
Study drug reconciled (MD)				•	•	•		•	•	•
Central Laboratory Measures										
Hematology and chemistry labs		•		•		•		•	•	•
HbA _{1c} (diabetics only) ⁿ		•								
Local Laboratory Measures										
Urine or serum pregnancy ^f		•								

	Screen	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visits 6, 8, 10, 12	Visits 7, 9, 11		Visit 13 / Final Visit
Procedure		Day 1 ^a	<u>Telephone Contact</u> Day 14 (±3 days)	Day 30 (±3 days)	Month 3 (±7 days)	Month 6 (±14 days)	<u>Telephone Contacts</u> Months 9, 15, 21, and 27 (±14 days)	Months 12, 18, and 24 (±14 days)	Early Disc. From Study Drug ^b	Month 30 / Disc. From Study
Platelet Function Substudy										
Predose Accumetrics VerifyNow® P2Y ₁₂ assay ^g		• ^h								
Postdose Accumetrics VerifyNow P2Y ₁₂ assay ^g		• ^h		• ⁱ	• ⁱ	• ⁱ		• ⁱ	• ⁱ	• ⁱ
Accumetrics VerifyNow® Aspirin assay		• ^j		•						
Biomarker measurements ^k		•		•		•			• ^k	• ^k
Genotyping for drug metabolism enzymes and transporters		•								
Health Outcomes Substudy										
EQ-5D questionnaire ^l		•			•			• (Visit 7 only)	•	•

Abbreviations: CK-MB = creatine kinase-MB fraction; Disc. = Discontinuation; ECG = electrocardiogram; IVRS = interactive voice response system; LD = loading dose; MD = maintenance dose; No. = number; NP = nurse practitioner; PA = physician's assistant; V = visit.

- a Visit 1 is to occur within 10 days of the onset of the index event.
- b Subjects prematurely discontinued from the study drug will have early discontinuation visit procedures performed upon withdrawal.
- c Subjects will supply their own daily aspirin therapy with the dose determined at the investigator's discretion. The recommended dose after discharge from the index hospitalization is 75 to 100 mg.
- d At Visit 1, subjects who are considered clopidogrel-naïve (have not received clopidogrel prior to the index event) or who are deemed to not be at steady state (that is, subjects who have received a maintenance dose of clopidogrel for <5 consecutive days immediately prior to the index event AND who have not received a commercial clopidogrel loading dose within 72 hours following the onset of the index event with administration of daily maintenance dose thereafter) will be randomized to either a clopidogrel 300-mg loading dose followed by 75-mg once-daily maintenance dose or prasugrel 30-mg loading dose followed by a 10-mg once-daily maintenance dose. Subjects ≥ 75 years of age or < 60 kg body weight at the time of randomization and who are randomized to prasugrel will receive prasugrel 30-mg LD followed by 5-mg once daily maintenance dose. The first dose should be given as soon as possible after randomization and up to 72 hours following the onset of the index event. Subjects who have received a commercial clopidogrel loading dose within 72 hours following the onset of the index event and daily maintenance doses thereafter or who have received ≥ 5 consecutive days of commercial clopidogrel immediately prior to the index event will be randomized to either clopidogrel 75-mg once-daily maintenance dose or prasugrel 10-mg once-daily maintenance dose. Subjects ≥ 75 years of age or < 60 kg body weight at time of randomization and who are randomized to prasugrel will receive a 5-mg once daily maintenance dose. The first dose of study drug for these subjects should be administered as soon as possible after randomization and up to 24 hours following the previous dose of commercial clopidogrel.
- e After the first dose of study drug, subsequent doses should be administered once daily and may be taken with or without food. For subjects participating in the platelet function substudy, the MD should be taken at least 2 hours prior to the planned outpatient visit.
- f A urine or serum pregnancy test will be performed locally for women of childbearing potential, and must be performed (with results reviewed) prior to randomization.
- g An additional platelet function measurement should be collected if a subject experiences an efficacy endpoint event or a bleeding event during the index hospitalization or at any time.
- h At Visit 1, the platelet function measurement should be obtained both prior to study drug and at 120 ± 10 minutes following administration of study drug.
- i The platelet function measurement should be obtained no less than 2 hours following administration of the daily MD.
- j At Visit 1, the VerifyNow® Aspirin assay should be obtained only prior to administration of the LD.
- k Biomarker measurements include hs-CRP and NT-proBNP (or BNP). At the early discontinuation from study drug visit or at the final discontinuation visit, biomarkers will be collected only if the subject discontinues from the study prior to Month 6.
- l Quality of life will be measured in all subjects using the EQ-5D (except at a small minority of sites where an appropriate translation of the questionnaire is unavailable), with additional selected measures in a subgroup of subjects. Quality-of-life surveys will be collected at baseline, 3 months, 12 months, and end of study.
- m Electrocardiograms not performed at Visit 9.

Prasugrel hydrochloride (LY640315)

Confidential

Protocol Amendment(b)

- ⁿ HbA_{1c} will be performed only on patients who are diabetic at baseline.
- ^o The directed physical exam must be performed by a physician, physician's assistant (PA), or nurse practitioner (NP).

Protocol Attachment TABY.2. Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology^a	Clinical Chemistry^a
Hemoglobin	Serum Concentrations of:
Hematocrit	Total and direct bilirubin
RBC count	Alkaline phosphatase
WBC	ALT/SGPT
Neutrophils, segmented	AST/SGOT
Lymphocytes	BUN
Monocytes	Creatinine
Eosinophils	Glucose, random
Basophils	Total cholesterol
Platelets	HDL cholesterol
	LDL cholesterol
	Triglycerides
	HbA _{1c} (in diabetic subjects) ^d
Additional Laboratories^b	
NT-proBNP (or BNP)	
hs-CRP	
Cytochrome P450 genotypes	
Pregnancy Test (females of childbearing potential only) ^c	

Abbreviations: ALT = alanine aminotransaminase; AST = aspartate aminotransaminase; BUN = blood urea nitrogen; HDL = high density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; LDL = low density lipoprotein; NT-proBNP = N-terminal prohormone brain natriuretic peptide; RBC = red blood cells; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; WBC = white blood cells.

^a To be performed at Lilly-designated central laboratories.

^b To be performed at Lilly-designated core laboratories.

^c To be performed at local laboratories.

^d HbA_{1c} will be performed only on patients who are diabetic at baseline.

For additional information, refer to the Study Schedule.

**Protocol Attachment TABY.3.
Health Outcomes Substudy**

Economic and Quality of Life Outcomes in TRILOGY ACS

TRILOGY ACS Health Outcomes (HO) H7T-MC-TABY Protocol

November 6, 2006

Updated August 16, 2007

Updated December 5, 2007

Updated January 31, 2008

Updated May 05, 2009

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I. INTRODUCTION

Despite a Class IA recommendation for early invasive management by the American College of Cardiology (ACC)/American Heart Association (AHA) and the European Society of Cardiology (ESC) guidelines, over 50% of patients presenting with unstable angina/non-ST-elevation acute coronary syndromes (UA NSTEMI ACS) across the world are managed medically [1-4]. Standard therapy for UA/NSTEMI ACS patients, including those managed medically, consists of a combination of aspirin and clopidogrel. However, significant rates of morbidity and mortality in this population despite current medical therapy suggest that there is room for new treatments in this patient population [1-2, 5]. Preliminary studies have found prasugrel hydrochloride, a novel thienopyridine adenosine diphosphate (ADP) receptor antagonist, to be associated with less variability in patient response compared with clopidogrel [6]. The purpose of the TRILOGY ACS study is to examine whether, compared with clopidogrel and aspirin, the use of prasugrel and aspirin is associated with a significant reduction in the risk of a combined endpoint of cardiovascular death, myocardial infarction (MI), or stroke.

This attachment outlines the objectives and design of the TRILOGY ACS Health Outcomes (TRILOGY ACS HO) substudy. The principal goal of TRILOGY ACS HO is to assess the economic and quality of life consequences of the two treatments being compared in the TRILOGY ACS study.

II. SPECIFIC AIMS OF TRILOGY ACS HO

The following are the specific aims pertaining to economic and quality of life outcomes in TRILOGY ACS HO:

Economic Specific Aims

1. To measure and compare cumulative total medical costs for the two treatment arms in TRILOGY ACS according to randomization treatment assignment (primary analysis will be in U.S. subjects).
2. To estimate the incremental cost effectiveness of the prasugrel arm relative to the

clopidogrel arm, assessed as cost per life year added and cost per quality-adjusted life year added.

3. To examine health care costs and resource use as a function of both treatment assignment and degree of platelet aggregation.

Quality of Life Specific Aims:

1. To compare health-related quality of life for the treatment arms according to randomization assignment.
2. To identify factors in addition to treatment assignment that are associated with variations in quality of life outcomes.

Increasingly, economic and quality of life outcomes have become integral components in the overall evaluation of new treatments. In the current era of restrained spending on health care, new therapies must not only produce evidence of efficacy but also must show that their extra or incremental health benefits are produced in proportion to their incremental costs in order to be acceptable for large scale implementation. In CURE, the standard therapy (clopidogrel) has been demonstrated to be cost-effective relative to placebo with a cost of \$6,318 per life year gained [7]. It is therefore essential that prasugrel demonstrate favorable economic and quality of life outcomes in order to be considered a viable treatment option in the UA/NSTEMI ACS population.

III. DESIGN OVERVIEW

The design of this substudy is based on the primary operating principal that nothing in the design or implementation of this substudy should impede the operation of the main TRILOGY ACS study with regard to investigator participation, patient enrollment, or ascertainment of study primary endpoints.

This proposal describes three main components of TRILOGY ACS HO: data collection, quality of life analyses, and cost-effectiveness analyses. The data collection activities include both the data to be collected as part of the main study (demographic and clinical descriptors, medical resource use, and medical outcomes) and the data to be collected

specifically for the substudy (cost, quality of life, and utility data).

The analyses according to randomization assignment will address the two of the five specific aims of the substudy (see Section II). The cost-effectiveness analyses will generate country-specific cost-effectiveness ratios and appropriate sensitivity analyses.

IV. STUDY POPULATION

It is estimated that a total of 10,300 subjects will be enrolled in TRILOGY ACS in 35 countries around the world. Eligibility criteria are described in the main study protocol. Table 1 summarizes the subjects to be enrolled in the various components of the Health Outcomes substudies. Informed consent for TRILOGY ACS HO substudy will be included in the overall TRILOGY ACS informed consent form used at the time of initial study enrollment. In addition, repeat verbal consent will be obtained at the time of each contact.

Table 1. Subjects enrolled in the economic and quality of life components of the TRILOGY ACS HO study

Description	Baseline and Follow-up (3M, 1Y, EOS)*	Data Collection Responsibility
Resource utilization in e-CRF	All subjects	Study site via e-CRF
Hospital billing data	All U.S. subjects	DCRI
Quality of life battery Survey**	All subjects enrolled in Western Europe (Austria, Belgium, Denmark, Finland, France, Germany, Italy, Netherlands, Portugal, Spain, Sweden, Switzerland, and UK), Australia, New Zealand, Czech Republic, Hungary, Poland, Canada, and U.S.	See Sec V.4 for details
EQ-5D in e-CRF	All subjects	Study site via e-CRF

* 3 months \pm 2 weeks; 1 year \pm 2 weeks; End of study

**survey = SF-12, MHI-5, SAQ Angina Frequency and Physical Function Scales, and Socioeconomic status (see Sec V.4)

V. DATA COLLECTION

V.1 Baseline Clinical/Demographic Data

Baseline data collection will consist of the demographic and clinical data contained on the main TRILOGY ACS case report form. These data, which include age, sex, cardiovascular risk factors, previous MI, previous angina, and presenting severity of illness, will be used in secondary analyses to examine the relationships between patient specific factors and economic and quality of life outcomes in TRILOGY ACS.

V.2 Medical Resource Use Data

Health care resource use will be collected on the main TRILOGY ACS e-CRF from enrollment to end of follow-up for all subjects in the study. Measures will include length of stay by intensity of care (ICU, stepdown, regular care), number of diagnostic cardiac catheterizations, number and type of percutaneous coronary revascularization procedures (PTCA, stent), and other selected diagnostic and therapeutic procedures.

After the initial hospitalization, the resources to be tracked include emergency department visits, outpatient cardiac rehabilitation visits, and re-hospitalizations. For each re-hospitalization, information pertaining to length of stay (total and ICU days), procedures (cardiac catheterization, PTCA/stent, CABG), and events that occur will be captured in the e-CRF.

V.3 Medical Cost Data For U.S. Perspective Analyses

For this substudy, we will attempt to assess U.S. medical care costs as accurately as possible. There are a number of important issues that must be considered in a medical cost analysis, including the way "costs" are to be conceptualized and measured, the time perspective of the analysis (that is, short run versus long run), and the payer perspective to be used (for example, societal, hospital, third party) [8-10]. Medical costs expressed in U.S. dollars (or another currency) are a convenient metric for valuing and aggregating the disparate resource inputs required to produce different medical care products and services [11, 12]. In a multi-country study such as TRILOGY ACS,

medical prices and associated resource inputs vary substantially from country to country (for example, U.S. versus Canada) and no single set of prices can therefore be selected as most appropriate for or representative of the study as a whole. Thus, country-specific cost weights will be applied to the resource quantities collected in this substudy with the U.S. cost analysis constituting the primary analysis.

There are two major types of costs that must be assessed in this study: hospital costs (including emergency department costs unassociated with hospital admission) and physician service costs. The options for measuring hospital cost in multicenter studies in the U.S. are limited by the level of detail available from individual participating hospitals.

Common denominator measures available from virtually all hospitals must therefore be used, rather than the most detailed data that only a few could provide (for example, those using microcosting systems). Thus, conversion of charges to costs using a top-down approach represents the "state of the art" for multicenter cost studies [10, 13]. For measurement of hospital costs, this study will collect hospital bills and emergency room visits on all U.S. subjects along with hospital-specific Medicare Cost Report RCCs [14]. To perform a charge to cost conversion on these bills, a uniform billing form (UB 92) will be obtained for each hospitalization and emergency room visit bill. The UB 92 claims form represents a common reporting format that all U.S. hospitals use and it contains a number of important data items, including ICD-9 diagnosis and procedure codes that can be used to assign a Medicare DRG to each hospitalization in order to perform a supplemental cost analysis from the Medicare perspective. The revenue center categories and codes on the UB 92 will be matched against those in the hospital's most recent Medicare Cost Report to calculate revenue center level costs, which will then be summed to yield total hospital costs.

For physician service costs in the U.S., we propose to enumerate major physician services directly from the main TRILOGY ACS case report form supplemented where necessary with the hospital billing data on procedures and assign physician service costs using the Medicare Fee Schedule, which provides a standardized resource-based

approach to costing out these services [15].

Medical Cost Data for Selected Other Countries

Cost analysis methods for selected other participating countries, including cost weight data collection, will be detailed in a supplemental document.

V.4 Quality of Life Data

Quality of Life:

As part of the TRILOGY ACS HO substudy, we will conduct a comprehensive assessment of subjects' quality of life that incorporates both generic and disease-specific measures. The QOL battery comprises the EQ-5D, which will be contained in the e-CRF, and a QOL survey (see Table 2). Administration timeline is outlined in Table 1. The baseline data will be completed following informed consent and prior to randomization / treatment. A brief description of the instruments follows.

Table 2. Battery of instruments proposed for the QOL assessment in TRILOGY ACS*

Instrument	Main outcome measure	# of questions	Approximate time needed to complete the questions
EQ-5D	Patient utilities	6	2 minutes
Short Form-12 (SF-12)	Functional status	12	4 minutes
MHI-5 (Mental health scale of SF-36)	Anxiety and depression	5	2 minutes
Angina Frequency and Physical Function Scales of the Seattle Angina Questionnaire	Angina symptoms and physical function	2 + 9	5 minutes
SES questions	Socioeconomic Status	3	2 minutes
Total		36	15 minutes

* Administered at baseline, 3 months, 1 year, and end of study.

Quality of life as measured by the EQ-5D: The EQ-5D consists of two parts: a 5 dimension assessment of “your own health state today,” which allows for definition of 243 discrete health states that can be mapped to population utility weights, and a self rating (0-100) “thermometer” of current health-related quality of life [16-18]. Patient preference weights, or utilities, for each of the 243 unique health states have been derived from the general population in the UK and more recently in the U.S. [19-23]. The overall quality of life measured by the EQ-5D will be one of three pre-specified major quality of life endpoints for TRILOGY-ACS. The utility measures derived from the EQ-5D will be used to quality-adjust survival and calculate a cost-utility ratio for prasugrel (incremental cost per quality-adjusted life year saved).

Overall health related quality of life measured by the SF-12: The SF-12 is a validated, abbreviated, short form (SF) version of the SF-36 which measures health

related quality of life. It retains the eight sub-scales of the SF-36 and has the important qualities of normative scale data and a comprehensive set of country translations.

Cardiac symptoms and physical limitations measured by sub-scales of the SAQ and the SF-36: Angina symptoms in the UA/NSTEMI ACS population have both clinical and quality of life implications. We have previously documented that the frequency of angina was higher among patients who did not undergo revascularization [24-25]. In the GUSTO-IIb study, 54% of patients who were medically managed, compared with 44% of patients who underwent revascularization, reported angina symptoms at one year follow up ($p < 0.01$). Given that the TRILOGY ACS population consists of medically managed UA/NSTEMI ACS subjects, we believe that it is important to assess the effect of prasugrel on this quality of life outcome. The **Seattle Angina Questionnaire** (SAQ) is a validated, disease-specific questionnaire with 5 summary scales as they relate to angina: physical limitations, angina stability, angina frequency, treatment satisfaction, and disease perception. The SAQ has been translated into approximately 26 languages. We propose the capture of 2 angina frequency items that will allow us to calculate the angina frequency scale and 9 items of the physical limitations scale which will augment the two SF-12 items measuring physical function. The SAQ physical function items will provide clinically important changes over time as a more sensitive disease-specific measure. Physical function will be the second of three pre-specified major quality of life endpoints for TRILOGY-ACS.

Psychological status: Several studies have shown that patients with anxiety and depression are at a higher risk of adverse events following acute myocardial infarction [26]. Data on the impact of psychological status on outcomes in the UA/NSTEMI ACS is more limited and we therefore propose to collect the MHI-5 in the TRILOGY ACS population to address this issue. The MHI-5 is the 5 item mental health index originally developed for the Medical Outcomes Study which became the SF-36 mental health sub-scale. It will be the third pre-specified major quality of life endpoint.

Socio-economic status: Three SES questions which we include in all of our QOL studies as part of the descriptive battery of items are: marital status, education, and

work. The work items were developed in 1988 from our first large randomized study (Bypass-Angioplasty Revascularization Investigation (BARI) Substudy in Economics and Quality of Life (SEQOL)).

Administration

The EQ-5D will be collected for all subjects (except at a small minority of sites where an appropriate translation of the questionnaire is unavailable) in the e-CRF at baseline and at 3 months, 1 year and EOS. The QOL survey will be administered to all subjects enrolled in Western Europe (Austria, Belgium, Denmark, Finland, France, Germany, Italy, Netherlands, Portugal, Spain, Sweden, Switzerland, and UK), Australia, New Zealand, Eastern Europe (Hungary, Czech Republic, and Poland), Canada, and the US. Site coordinators will administer the baseline QOL survey in all countries. In non-North American countries, site coordinators will also administer the follow-up QOL survey and fax the questionnaire to DCRI. In North America, follow-up QOL interviews will be performed centrally by the Duke Economics and Quality of Life (EQOL) Coordinating Center Staff based on patient contact information collected by the site coordinators at baseline (see Table 1). The baseline survey will be administered after consent and before randomization. For follow-up interviews, the target window will be ± 2 weeks from the follow-up date (3 months, one year, and EOS).

The QOL battery has been designed to provide a comprehensive assessment of patients' quality of life while keeping the burden and cost of data collection to a minimum. The EQ-5D is incorporated in the e-CRF and can be administered in approximately two minutes. The QOL survey is four pages long and should take approximately 15 minutes to complete. The proposed time points for QOL assessments (baseline, 3 months, 1 year, and EOS) have been selected to coincide with follow-up visits scheduled as part of the clinical study.

EQ-5D data will be reviewed for completeness and analyzed by the DCRI EQOL Coordinating Center in conjunction with data imports from the CRO. All other QOL Questionnaire data forms will be supplied, centrally reviewed, database entered, Q/Ced, and analyzed by the DCRI EQOL Coordinating Center.

VI. DATA ANALYSES

Data analysis for this project will involve two major components: analyses according to randomization assignment and cost-effectiveness analyses. The reports generated from this substudy will present as much relevant empirical data as possible, along with the associated lifetime projections used in cost-effectiveness analysis, to allow readers to judge the reasonableness of the overall results of the analyses.

VI.1 Analyses According to Randomization Assignment

To achieve the first major goal of this substudy, we will perform analyses comparing subjects according to randomized treatment assignment. The primary analyses will be restricted to subjects enrolled in the U.S. Economic endpoints will include total medical costs for the baseline hospitalization, cumulative one-year medical costs, and cumulative medical costs for the duration of enrollment in the study. For testing of discrete variables, contingency table chi-square tests or Fisher's exact tests will be used. For testing of continuous variables, nonparametric statistical tests will be used, such as the Wilcoxon rank-sum test. To examine the major determinants of study outcomes including the interrelationships of baseline clinical characteristics and economic outcomes, regression models will be employed (for example, logistic regression for binary outcomes, Cox model for time to failure outcomes, multivariable linear regression for continuous outcomes). In each case, preliminary steps will be taken to ensure that the assumptions of the model are appropriately satisfied. Statistical comparisons will follow the precedents established in the clinical protocol.

VI.2 Cost-Effectiveness Modeling

The second major goal of this substudy is to perform a cost-effectiveness analysis of prasugrel and aspirin versus clopidogrel and aspirin. Cost effectiveness refers to a family of techniques for economic analysis that provide a structured format for relating health care resource utilization (costs) to health care outcomes (efficacy) [27]. A major goal of cost-effectiveness analysis is to provide policy and other health care decision makers with the information needed to allocate scarce health care resources in the most efficient

manner possible [28,29]. Current projections are that TRILOGY ACS will involve approximately 35 countries and a total enrollment of 10,300 subjects with approximately 2500 subjects enrolled in the U.S. Because of substantial differences in the health care systems of the U.S., Canada, and the European participants, there is no meaningful global cost-effectiveness analysis for TRILOGY ACS that can be performed. Instead, the overall clinical results of TRILOGY ACS must be combined with country-specific cost weights to generate relevant country-specific cost-effectiveness ratios. This proposal describes such an analysis for the U.S. A similar analysis is envisioned for the non-U.S. participants.

VI2.1. The Core Cost-Effectiveness Model

For the present analysis, the core cost-effectiveness model will be defined to the extent possible by starting parameters (the base case model) from the empirical results of the overall TRILOGY ACS study and, when appropriate, the economic substudy. The principal analysis will employ a societal perspective (although not all societal costs will be included). Costs will be expressed in current U.S. dollars. Secondary analyses will use the Medicare perspective and the hospital perspective.

Two main parameters are required for the core base case model: incremental life expectancy and the incremental costs. "Incremental" in this context refers to those added health benefits or costs derived by shifting the TRILOGY ACS cohort from the clopidogrel arm to the prasugrel arm. Estimation of incremental life expectancy is difficult because TRILOGY ACS has been designed with the explicit recognition that the study sample size will not be sufficient to detect the likely treatment effect on mortality alone. Since many of the events prevented by prasugrel are likely to be nonfatal MIs or nonfatal strokes, the economic substudy must have a method for translating the effects of these events in the two groups into mortality/life expectancy differences. Therefore, assuming that the superiority of prasugrel over clopidogrel is established, we propose to use registry and clinical study data available to the DCRI Outcomes Group to model the effects of nonfatal MI and nonfatal stroke on subsequent cardiovascular death. In the cost-effectiveness analysis of the PURSUIT trial, we

estimated that a nonfatal MI had about 1/8th the impact on life expectancy of a death in this population [30]. The principal analysis tool for this work will be the Cox proportional hazards regression model with time-dependent covariates. The basic goal of the analysis will be to project long-term survival for the cohorts described above using nonfatal MI and nonfatal stroke as model covariates rather than an outcome event. This model will then be applied to the TRILOGY ACS study cohort.

The TRILOGY ACS study will provide empirical event-free survival data for a median of 18 months following treatment. Since cost-effectiveness models are typically based on incremental life expectancy, a method is required to convert these survival rates into life expectancy estimates. For this study, we will use a method for estimation of life expectancy that provides a covariate adjustable life expectancy estimate. This method, which was employed in the PURSUIT cost-effectiveness analyses [30], involves modeling the long-term post study survival experience of TRILOGY ACS subjects using the long-term follow-up data in secondary data sources available to the DCRI Outcomes Group.

- 1) Using Cox Proportional Hazards regression methodology for left truncated and right-censored data, we will model the hazard of death as a function of age, adjusting for additional prognostic factors through covariates. This model “adjusts for” age as the metric over which the hazard is computed and treats additional prognostic factors as co-variables. By estimating the hazard over the age metric (rather than over the time metric, as is traditionally done) we can produce data-based survival predictions through a much longer time period due to the anticipated broad representation of ages that will be represented in the TRILOGY ACS database. The hazard relationship, which under proportional hazards is well estimated through the age range represented in our data, will be used for prediction on a patient by patient basis.
- 2) Again using a Cox Proportional Hazards regression model, together with the extensive post-MI survival experience available secondary data sources, we

will estimate the long-term survival impact of a nonfatal MI and nonfatal stroke in UA/NSTEMI ACS subjects. This model will provide a measure of the increased relative risk attributable to an MI and a stroke for later incorporation in the individual subject predictions.

- 3) The observed survival experience in the TRILOGY ACS study will be modeled to ensure that estimated differences in life expectancy are based solely on treatment-effect differences and not on covariate imbalances that may exist between the survivors in each treatment group. This survival model will stratify on treatment group (if necessary to satisfy the proportional hazards assumption) and adjust for other significant predictors of survival within the TRILOGY ACS follow-up period.
- 4) Finally, using the models described above, we will produce a covariate-specific lifetime survival prediction for each patient. The individual predicted survival estimates will be averaged over all subjects for both treatment groups to produce a mean predicted survival estimate for each treatment group. The estimated mean survival curves will then be integrated over a lifetime to obtain mean life expectancy for each treatment group. Differences between the area under each survival curve will be computed to obtain the incremental life expectancy due to the investigational treatments. All the major steps in this methodology have been successfully used in the PURSUIT cost-effectiveness analysis [30]. Future life expectancy will be continuously discounted at an annual rate of 3% [13].

Cost per quality-adjusted life year will be calculated using the estimated life expectancies described above together with the measured 1 year utility weights.

One important set of sensitivity analyses will examine the effect on the cost-effectiveness ratio of varying the incremental life expectancy within a plausible range (for example, based on the 95% confidence limit of the observed survival difference between prasugrel and clopidogrel patients).

In addition, we will examine the impact of varying each of the starting parameters over a clinically plausible range. Threshold values for each parameter will be sought that yield cost-effectiveness ratios of \$50,000 and \$100,000 per life year added. For the life expectancy parameter, four variations will be explored: a) variations in the initial 3-month benefits of treatment using the 95% confidence limits of the observed difference in event rates, b) variations in the extent of long-term survival benefits, and c) variations in the relationship between nonfatal MI and subsequent survival; d) variations in the relationship between nonfatal stroke and subsequent survival. For the incremental cost parameter, two components must be considered: the incremental cost of the assigned drug therapy (essentially the cost of prasugrel) and the incremental difference in induced medical costs (and savings). If a price has not been set for prasugrel at the time of the analysis, potential price values as defined in conjunction with the sponsors will be explored. Price parity with clopidogrel is one logical scenario. The sensitivity analysis of the incremental cost differences, other than those due to the drug under study, will be based on the 95% confidence limits around the observed cumulative cost differences.

VII. HUMAN SUBJECTS

Sources of Material: All economics and quality of life data are entered into a secured SQL Server database archived and analyzed by the Economics and Quality of Life Coordinating Center (EQOL CC). All economic and quality of life data will be identified by the unique, clinical subject number, and all information received by the EQOL CC will have subject identifiers removed (hospital bills) except for confidential patient information which includes, for example, the subject's name, address and phone number in order to perform telephone follow-up quality of life interviews (U.S. and Canadian sites only) and collect hospital billing information (U.S. sites only). These personal health identifiers are stored by the EQOL CC in a separate, secure database from the e-CRF with strict enforcement of restricted access. This process meets all HIPAA requirements.

VIII. TIME LINE, WORK PLAN, AND WORK PRODUCT

It is proposed that initial economic results from this substudy related to the potential cost saving effects of prasugrel will be ready for presentation in conjunction with the principal medical results from the study. A preliminary cost-effectiveness model will also be delivered at that time.

The principal deliverables from this project will be papers to be submitted to peer-reviewed journals describing the results of these analyses. A paper describing the U.S. results will be completed one-year following the completion of study clinical follow-up. Cost analyses specifically for other countries or regions of the world will be identified in collaboration with the sponsor and the steering committee and undertaken. All publications submitted using TRILOGY ACS data must be approved in advance by the TRILOGY ACS Steering Committee. In addition, any manuscripts being prepared for publication will be submitted to the study sponsor prior to submission for review and comment.

The relationship of the investigators in this substudy with the sponsor will be in accordance with the guidelines proposed by medical journal editors [31]. Specifically, study data and study analyses will be controlled by investigators who are independent of the sponsor. Any reports from the TRILOGY ACS economic substudy must be submitted to the sponsor for review and comment prior to submission to a journal. However, responsibility for final content of each publication will reside with the PIs of this substudy and the TRILOGY ACS Steering Committee.

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Protocol Attachment TABY.4.
New York Heart Association Congestive Heart Failure
Classifications

- Class I: patients with no limitation of activities; they suffer no symptoms from ordinary activities.
- Class II: patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.
- Class III: patients with marked limitation of activity; they are comfortable only at rest.
- Class IV: patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

Source: [NYHA] New York Heart Association. 1994.

1. Title Page

**Statistical Analysis Plan:
A Comparison of Prasugrel and Clopidogrel in Acute
Coronary Syndrome (ACS) Subjects with Unstable
Angina/Non-ST-Elevation Myocardial Infarction (UA/NSTEMI)
Who are Managed Medically – The TRILOGY ACS Study**

LY640315 (Prasugrel hydrochloride)

Study H7T-MC-TABY is a Phase 3, multicenter, randomized, parallel-group, double-blind, double-dummy, active-controlled study in subjects who have experienced recent (within 10 days) non-ST-elevation acute coronary syndrome (NSTEMI ACS) and who are to be managed medically.

Eli Lilly and Company
Protocol H7T-MC-TABY
Phase 3
SAP Version 2

Confidential Information

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Statistical Analysis Plan approved by Lilly: 27 August 2009
Statistical Analysis Plan Version 2 electronically signed and approved by Lilly on date provided below.

Approval Date: 07-May-2012 GMT

2. Table of Contents

Section	Page
1. Title Page.....	1
2. Table of Contents.....	2
3. Revision History	5
4. Study Objectives	6
4.1. Primary Objective	6
4.2. Secondary Objectives	6
4.2.1. Efficacy Objectives	6
4.2.2. Safety Objectives	6
5. A Priori Statistical Methods	8
5.1. General Considerations	8
5.2. Efficacy Analyses	9
5.2.1. Primary Outcome and Methodology	9
5.2.2. Additional analyses of the primary endpoint.....	10
5.2.3. Secondary Efficacy Outcomes.....	13
5.3. Handling of Dropouts or Missing Data.....	17
5.4. Multicenter Studies	18
5.5. Multiple Comparisons/Multiplicity.....	18
5.6. Subject Disposition	19
5.7. Subject Characteristics	20
5.8. Treatment Compliance	25
5.9. Concomitant Therapy.....	25
5.10. Safety Analysis	25
5.10.1. Safety Endpoint Analyses.....	25
5.10.2. Adverse Event and Laboratory Analyses	28
5.10.3. Neoplasm analyses.....	29
5.11. Subgroup Analysis	31
5.11.1. Patient Characteristics	31
5.11.2. Baseline history/conditions	32
5.11.3. Medications	33
5.11.3.1. Medications used during index hospitalization.....	33
5.11.3.2. Aspirin Use	33
5.11.3.3. Concomitant Medications at time of randomization	33
5.11.3.4. Proton pump inhibitors (PPI)	34
5.12. Adjustments for Covariates	34

5.13. Platelet Function Substudy	35
5.13.1. Platelet Aggregation Baseline Characteristics	36
5.13.2. Platelet Aggregation as Predictor of Outcome	36
5.13.3. Comparison of treatment groups of PA	37
5.13.4. Subgroup analysis of PA for those patients previously treated with Clopidogrel	37
5.13.5. Bleeding and PA	38
5.13.6. ROC Analysis	38
5.13.7. Multivariate Predictive Model	38
5.13.8. Poor Responder Analysis	38
5.13.9. Comparison of Prasugrel Formulations	39
5.13.10. Subgroup Analyses	39
5.13.11. Biomarker Measurements	39
5.13.12. Aspirin Assay	39
5.13.13. Aspirin assay combined with PRU	40
5.14. Genomics Substudy	40
6. References	41
7. Appendices	42

Table of Contents

Appendix	Page
Appendix 1. Study Drug Treatment by Commercial Clopidogrel Status.....	43
Appendix 2. Calculation of the GRACE score	44

3. Revision History

Study H7T-MC-TACY (TRILOGY ACS Study) Statistical Analysis Plan Version 1 was approved prior to DMC interim analysis that occurred on August 29, 2009.

Version 2 includes additional details and analyses and was approved prior to database lock.

4. Study Objectives

4.1. Primary Objective

The primary objective of this study is to test the hypothesis that prasugrel and aspirin is superior to clopidogrel and aspirin in the treatment of medically managed subjects enrolled within 10 days of the unstable angina/non-ST-segment elevation myocardial infarction (UA/NSTEMI) index event. Superiority will be assessed by the reduction in risk of the composite endpoint of first occurrence of cardiovascular (CV) death, myocardial infarction (MI), or stroke throughout the study.

The primary analysis will be conducted in a hierarchical manner, with evaluation of the primary endpoint performed first in medically managed subjects < age 75 years. Conditional on successfully establishing superiority in the primary analysis, the same composite endpoint will be evaluated in the entire population.

4.2. Secondary Objectives

The following secondary endpoints will be analyzed in both the population of medically managed subjects age <75 years, the entire medically managed population (subjects of all ages) as well as those patients ≥ 75 years of age. No hierarchy will be applied to the secondary endpoints since they are highly correlated with the primary and therefore will be considered supportive in nature.

4.2.1. Efficacy Objectives

Secondary efficacy objectives are to compare the prasugrel and clopidogrel groups with respect to:

- The risk of the composite endpoint of first occurrence of CV death and MI.
- The risk of the composite endpoint of first occurrence of CV death, MI, stroke, or rehospitalization for recurrent UA.
- The risk of the composite endpoint of first occurrence of all-cause death, MI, or stroke.
- The risk of first occurrence of stent thrombosis.

Components of the primary and secondary composite endpoints will also be analyzed individually as described in Section 5.

4.2.2. Safety Objectives

In subjects receiving prasugrel or clopidogrel, the safety objectives are to evaluate the incidence of:

- Non-coronary artery bypass graft (non-CABG)-related TIMI life-threatening bleeding.
- Non-CABG-related TIMI major bleeding.

- Non-CABG-related TIMI major or minor bleeding.
- Non-CABG-related TIMI major, minor, or minimal bleeding.
- Non-CABG-related Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) severe or life-threatening bleeding.
- Non-CABG-related GUSTO severe or life-threatening bleeding or moderate bleeding.
- Non-CABG-related GUSTO severe or life-threatening, moderate, or mild bleeding.
- Fatal bleeding or intracranial hemorrhage (ICH).
- CABG-related bleeding.

AND

- To evaluate the overall safety and tolerability (based on vital signs, laboratory values, incidence of new non-benign neoplasms, the occurrence of treatment-emergent adverse events including adverse events meeting the regulatory definition of a serious adverse event and those events leading to permanent discontinuation of study drug) in subjects receiving prasugrel or clopidogrel.

5. A Priori Statistical Methods

5.1. General Considerations

All analyses described below will be carried out in three cohorts:

- 1) subjects <75 years of age,
- 2) all subjects, and
- 3) subjects ≥ 75 years of age.

Subjects will be randomized at the country level, with stratification by age (<75 and ≥ 75 years) and commercial clopidogrel status (see Appendix 1 Table TABY.1 for the definition commercial clopidogrel status). Commercial clopidogrel status will be determined by questions 1 through 3 from eCRF form 050: Question 1 is “Did subject receive a maintenance dose of commercial clopidogrel for at least 5 continuous days prior to presentation”, Question 2 is “Did subject receive a loading dose of commercial clopidogrel within five days prior to presentation” and Question 3 is “Did subject receive a dose of commercial clopidogrel in the first 24/72 hours following presentation”. Note that 24 hours was changed to 72 per amendment B of protocol. Stratum 1 is defined as answering No, No, No to the three questions with an indication that a loading dose of study drug was given per form 160. Stratum 2 is defined as No, No, Yes. Stratum 3 is defined as Yes to question 1 or No to question 1 but Yes to question 2.

Primary analyses will be conducted on Clinical Endpoints Committee (CEC) adjudicated endpoints. Specific definitions of efficacy and safety endpoints are included in the protocol as well as the CEC Charter. In the composite endpoint analyses, reaching any component of the composite endpoint will be considered as reaching the composite endpoint. In analyzing non-composite endpoints, reaching only the specific endpoint will be considered (whether or not it is the first endpoint to occur).

Two key datasets are of interest: the ITT set consisting of all randomized subjects and the treated set consisting of subjects receiving at least 1 dose of study drug (including the loading dose). Efficacy endpoint analyses will be carried out using the ITT set. Efficacy endpoints that occur after discontinuation of the study drug will be included in the efficacy analysis unless otherwise specified.

Safety endpoint analyses will be carried out using the treated set. The focus of the safety analyses is any safety event (including bleeding events, treatment-emergent adverse event, or abnormal laboratory value) that occurred in a treated subject while “at risk.” A subject will be classified as “treated” if they receive at least one dose of study drug, either a loading dose or maintenance dose. A subject will be considered “at risk” during the period from the administration of the first dose of study drug up through 7 days after permanent study drug discontinuation, or the subject’s discontinuation visit, whichever is earlier. If an adverse event is classified by the investigator as “study drug related”, it will be considered part of the “at risk” set, regardless of the timing. Safety events that occur after 7 days of permanent discontinuation

of study drug and that are not considered related to study drug will not be included in the analyses but will be reported separately.

Time-to-event is defined as the time from randomization to the onset of the endpoint. Time to first event for a composite endpoint is defined as the time from randomization to the occurrence of the first event of the composite endpoint. Comparison of the treatment groups relative to primary and secondary efficacy endpoints will be carried out using time-to-first event analysis via a stratified two-sided log-rank test. The stratification variable consists of the 3 levels as given in Table TABY.1 (see Appendix). This stratification is being performed so that any possible bias related to switching subjects with prior commercial clopidogrel exposure to prasugrel may be evaluated. The stratification variable of age (<75 , ≥ 75 years) will also be used when analyzing all patients together. The p-value from the log-rank test will be considered the primary p-value for determining significance in time-to-event analyses. In addition to the reported p-value from the stratified log-rank test, Kaplan-Meier curves will be shown, and hazard ratios will be given along with a 95% confidence intervals. Available information on the vital status of subjects lost to follow-up or who withdrew consent will be included in the analyses of the all-cause death endpoint.

The potential influence of baseline risk factors will be assessed in an exploratory manner using the Cox proportional hazards model (see section 5.12). Comparison of the proportions of events will be carried out using Pearson's uncorrected chi-square test of homogeneity. Investigator or site effect on the treatment difference will not be assessed.

For various outcomes, confidence intervals for hazard ratios (under the assumption of proportional hazards) and/or relative risks will be provided. All confidence intervals will be 2-sided with a 95% confidence level, and all hypothesis tests will be 2-sided carried out at a significance level of 0.05.

Four sites in India were discontinued from participation in TRILOGY due to findings of non-compliance with Good Clinical Practice requirements which was revealed during site monitoring and auditing. There were findings of misconduct including suspected falsification of records. Study drug was stopped in all patients enrolled in these sites. Data from these 4 sites will not be expunged from the database, however all analyses (with the exception of sensitivity analyses) will be done excluding patients from these 4 sites. The site numbers are 25062, 25356, 25359 and 25065. Sensitivity analysis on the primary efficacy and primary bleeding outcomes will be done that includes data from these 4 sites.

5.2. Efficacy Analyses

5.2.1. Primary Outcome and Methodology

The primary endpoint is the composite of CV death, MI, or stroke in patients <75 years of age. Time from randomization to the first occurrence of the primary endpoint (CV death, MI, or stroke, whichever occurs first) will be compared between treatment groups using a stratified two-sided log-rank test where the strata are commercial clopidogrel status as defined in Table TABY.1 (see Appendix 1). Corresponding survival curves will be estimated by the

Kaplan-Meier method and two-sided 95% confidence intervals for the average hazard ratio will be provided with the use of the Cox proportional hazards model. The following information will be presented in a table for each treatment group: N, n (count of pts with event), %. Hazard ratio with 95% confidence interval will be given along with the p-value from stratified log-rank test. Kaplan-Meier curves and estimates of event rates will be provided at 30 days, 6, 12, 18, 24 and 30 months. The hazard ratio will be obtained from a Cox regression model with treatment and the stratification variable as fixed effects. Number needed to treat (NNT) will be reported based on the Kaplan-Meier estimates.

Primary analyses will be carried out in a hierarchical manner. At the first step, treatment groups will be compared within the <75 year old subjects using methodology above. Conditional on successfully establishing superiority of prasugrel over clopidogrel in the <75 year old subjects, treatment groups will be compared on all subjects using a stratified two-sided log-rank test with two stratification variables (commercial clopidogrel status as defined in Table TABY.1 and age: <75, ≥75 years). In addition, analysis for the primary outcome will be presented for those ≥ 75 years of age.

5.2.2. Additional analyses of the primary endpoint

Note that analyses of the primary endpoint for subgroups are described in section 5.11 and multivariate analysis are in section 5.12.

As a sensitivity analysis to the primary outcome, a Cox proportional model for time to first occurrence of the composite endpoint will be done with the following covariates included: age (as a continuous measure), NSTEMI vs. UA, diabetes (yes/no) and CrCl (Creatinine clearance as a continuous measure calculated by Cockcroft-Gault formula).

Those specific events that make up the primary composite endpoint will be broken down into mutually exclusive components (CV death, nonfatal MI, nonfatal stroke) with percentages given for each treatment group and compared between treatment groups with a Cochran-Mantel-Haenszel chi-square stratified by commercial clopidogrel status. Note that this is different from the analysis described below in section 5.2.3 for individual components. For this analysis, patients can not be in more than 1 category as the goal is to describe those events that composed the primary efficacy outcome.

An analysis will be done on the primary efficacy endpoint using only those patients that have been treated and are still on study drug during the “at risk” period. A subject will be considered “at risk” during the period from the administration of the first dose of study drug up through 7 days after permanent study drug discontinuation, or the subject’s discontinuation visit, whichever is earlier.

To encompass repeated events, an Anderson-Gill intensity model will be used. This type of model will use all available primary events, e.g., if a patient has 2 MIs and then dies, all three events will be included. Within this repeated events model, a “landmark” analysis will also be performed. This analysis will look at the treatment effect before and after a point in time and estimate the HR for both time periods. The effect seen prior to the specified point in time and

the effect seen after the point may then be compared to see if the treatment effect is different between these two time periods. Also included in this model will be the covariates of age, clopidogrel strata, NSTEMI vs. UA, diabetes (yes/no) and CrCl (as a continuous measure calculated by Cockcroft-Gault formula). The points of time of interest are 30 days, 6 months and 1 year. The Anderson-Gill model will also be repeated for those patients on study drug or within 7 days of discontinuing.

To test the effect of differing times from symptom onset to either first study drug dose or clopidogrel treatment, the following analyses will be done for the primary efficacy outcome:

- Within stratum 1 (LD of study drug received within 72 hours) the effect of the timing of loading dose will be explored in a Cox regression model with the following effects: time from first medical contact to loading dose, randomized treatment, time from first medical contact to loading dose by treatment interaction (which will test whether effect of the time of the LD on efficacy differs depending on which treatment was loaded), age strata. In addition, the analyses will be repeated using time of symptom onset to loading dose—note that symptom onset=CRF field of “time that last episode of symptoms started before presentation for evaluation of index event” but will be referred to as symptom onset for ease of reference. First medical contact is the CRF field with the question “When did the subject present for evaluation of the index event?”
- Within stratum 2 (LD of clopidogrel received within 72 hours), a similar analysis will be done to investigate the effect of timing of LD of commercial clopidogrel. A Cox regression model will include: time from first medical contact to loading dose, randomized treatment, time from first medical contact to loading dose by treatment interaction, age strata. Analyses will be repeated using time from symptom onset to loading dose.
- Within stratum 2 (LD of clopidogrel received within 72 hours), an analysis will be done to test whether the timing of randomization has an effect on efficacy. That is, when the patients “switched” from clopidogrel to study drug. A Cox regression model will include: time from LD of clopidogrel to time of first MD of study drug, randomized treatment, interaction between time from LD to MD and treatment, age strata.
- Within stratum 3 (steady state on chronic clopidogrel), an analysis will be done to investigate whether the timing of randomization has an effect on efficacy. That is, when the patients “switched” from clopidogrel to study drug. A Cox regression model will include: time from 1st medical contact to time of MD, randomized treatment and the interaction between time from symptom onset to time of MD and treatment, age strata. Analysis will be repeated using time of symptom onset.
- Additional exploratory models may be used.

In addition to the models listed above exploring effect timing of dose, the data will also be analyzed in a categorical fashion with N, n (count of pts with event), %. Hazard ratio with 95% confidence interval will be provided within each category. For example, in the first bullet listed

above, patients will be divided into groups by whether they received LD within 24 hours, 24-48 and 48-72. An interaction between these categories and treatment will be tested in the analysis model.

A sensitivity analysis on the primary endpoint will be done censoring patients at the time of their PCI or CABG if they have one during the study period. By doing this, only those events that occur prior to a revascularization (for those patients who had one) along with those events that occur in patients that did not have a revascularization will be included in the analysis. Finally, a sensitivity analysis will be done that will include region in the model in addition to the two other stratification variables.

A new formulation of prasugrel HCl was implemented between January 28 2010 and Sept 13, 2010. In order to assess whether this new formulation has an effect on the primary efficacy outcome, an analysis will be conducted with a Cox regression model with a time dependent covariate that indicates when the switch is made will be included in an analysis. For example, this variable will be set to 0 for the old formulation and then to 1 for the new formulation at the time when an individual switches to the new formulation. Keep in mind that while this switch will occur at the same calendar time, it will occur at different relative times for patients. There will be some patients that will only be on the old formulation, some that have switched from the old to the new, and some that will start on new formulation. However, an analysis of this type will enable us to test whether there is any difference between the two formulations, although the power will be low for such an analysis. In addition, an analysis for only those patients randomized with the new formulation will be carried out.

An analysis will be done to compare the efficacy for those patients randomized under the original protocol (A) to those randomized under the amended protocol (B). This analysis will be conducted with a Cox proportional hazards model with treatment, protocol under which the patient was randomized (original or amendment B) and the interaction between treatment and protocol. Stratification variables will also be included.

The sponsor will evaluate the proportionality assumption of the log-rank test by examining log-log survival plots. In addition to examining the log-log survival plots, the sponsor will also evaluate the assumption within a Cox proportional hazard model by adding a time-dependent covariate representing the interaction between treatment and time. If this interaction is significant, then there is evidence of non-proportionality. However, the model with the interaction incorporates the non-proportionality, and therefore, one could test for the treatment effect from this model. This analysis will be used as a sensitivity analysis; the primary pre-specified analysis will be the stratified log-rank test as outlined above.

An analysis of the primary efficacy endpoint comparing treatment groups will be done for those events occurring after premature study drug discontinuation.

The prasugrel effect on the primary composite endpoint of vascular death, myocardial infarction (MI) or stroke will be analysed according to a weighted time-to-event approach, as a secondary pre-specified analysis. This analysis will efficiently incorporate the differential value of all events in each patient in contrast to the more commonly applied time to first event analysis.

[Bakal et al, Armstrong et al] The TRILOGY steering and executive committees will be surveyed for their assessment of the relative weight of the individual components in the composite endpoint, and these responses will be used to derive the individual weights. And finally, the ‘trade-offs’ of each component of the efficacy composite with non-ICH bleeding, the key safety endpoint, will be assessed. These weights and trade-offs will be finalized prior to the lock of the databases.

In parallel, the primary efficacy composite will also be examined according to the win-ratio approach. [Pocock et al] Patients randomized to prasugrel will be matched, according to like risk profiles, to those randomized to clopidogrel. The matching will be based on the Global Registry of Acute Coronary Events (GRACE) Risk Score for 6-month death, which includes age, heart rate, systolic blood pressure, creatinine, Killip class, cardiac arrest at admission, ST-segment deviation, and elevated cardiac enzymes/biomarkers. [Fox KAA et al.] Within each matched pair, the prasugrel patient will be labeled as a ‘winner’ or ‘loser’ depending on who died from cardiovascular causes first; if neither patient died, then the matched pair is tested against the first occurrence of MI; and finally, if no assignment is made through CV death or MI, then they are tested against stroke. A provision will also be made to reorder the priority of MI and stroke.

5.2.3. Secondary Efficacy Outcomes

The following secondary efficacy endpoints will be assessed in the same fashion as the primary outcome measure, as described above in section 5.2.1, i.e., time to event will be compared between treatment groups with statistics provided as outlined above along with KM curves etc. Each one will be tested at $\alpha=0.05$. No hierarchy will be applied. The following analyses will be done for 3 cohorts of interest: <75 year olds, all patients and ≥ 75 year olds. The analysis of the events below will be based on adjudicated events.

- Composite endpoint of CV death and MI.
- All cause death and MI
- Composite endpoint of all-cause death, MI, or stroke.
- Composite endpoint of CV death, MI, stroke, or rehospitalization for recurrent UA.
- Composite endpoint of all-cause death, MI, stroke, GUSTO severe/life threatening bleed. In addition, two more analyses will be done. One in which non-CABG related TIMI life-threatening bleed will be used instead of the GUSTO defined bleed and one in which non-CABG related TIMI major bleed will be used.
- The following individual endpoints will also be assessed using the same methodology as above. Note that in analyzing these non-composite endpoints, reaching only the specific endpoint will be considered, therefore, patients could be counted in multiple categories. For example, if a patient had an MI followed by a stroke, in the analysis of the stroke individual outcome, the time to event will be time to the stroke, whereas in the analysis of the MI, time to event will be time to the MI.

- All MI
- All Stroke
- CV death
- All cause death
- Rehospitalization for recurrent UA
- Any coronary revascularization (PCI or CABG).
- Definite or probable stent thrombosis in all stents, i.e., either stents placed during study or previously in place prior to entering study.

In addition to the analyses listed above based on adjudicated events, the primary efficacy analysis, composite secondary efficacy outcomes as well as individual outcomes listed above will also be analyzed using the endpoint as reported by the investigator. Note that the investigators filled out an endpoint CRF titled “Severe Recurrent Ischemia”. This endpoint form was to be used for either myocardial infarction or a re-hospitalization for unstable angina. While the CEC was specifically asked which of these two endpoints were met, the investigator was not asked to sub-classify the recurrent ischemia as either an MI or unstable UA. However, the investigator was obligated to report the event as an adverse event and to indicate the specific event on the endpoint form. Therefore to determine whether an event is an “investigator reported MI”, we will first determine if the endpoint form was filled out, and then look to see whether one of the following of the preferred terms was recorded as the adverse event (or within 48 hours):

- ACUTE MYOCARDIAL INFARCTION
- MYOCARDIAL INFARCTION
- PAPILLARY MUSCLE INFARCTION
- SILENT MYOCARDIAL INFARCTION
- POST PROCEDURAL MYOCARDIAL INFARCTION
- CORONARY ARTERY EMBOLISM
- CORONARY ARTERY OCCLUSION
- CORONARY ARTERY THROMBOSIS
- CORONARY ARTERY REOCCLUSION
- CORONARY BYPASS THROMBOSIS

The investigator reported endpoint of “rehospitalization for recurrent ischemia” will be determined using the same process as above for MI. The patient will be required to have been hospitalized according to the endpoint form with one of the following preferred terms:

- ANGINA UNSTABLE
- MYOCARDIAL ISCHAEMIA
- ACUTE CORONARY SYNDROME
- POSTINFARCTION ANGINA
- PRINZMETAL ANGINA
- ARTERIOGRAM CORONARY
- ELECTROCARDIOGRAM ST SEGMENT DEPRESSION
- ELECTROCARDIOGRAM T WAVE INVERSION

- ELECTROCARDIOGRAM ABNORMAL
- ELECTROCARDIOGRAM ST SEGMENT ELEVATION
- ECG SIGNS OF MYOCARDIAL ISCHAEMIA
- ELECTROCARDIOGRAM REPOLARISATION ABNORMALITY

A comparison of events reported by the investigator to how they were adjudicated will also be done, i.e., whether each event reported by the investigator was positively or negatively adjudicated.

Details of efficacy endpoints:

- Cause of death summary: The two treatment groups will be compared using a stratified log rank test for the cause of death for cardiovascular reasons and non-cardiovascular reasons. Comparisons will not be made between treatment groups for individual causes of death due to small sample sizes that would be expected – but a frequency will be provided for each reason.
- A comparison between treatment groups, using the primary methodology, will be done for MIs defined as follows:
 - MIs using universal definition.
 - Combine Types 1 and 2 (spontaneous MIs per Question 35 CRF 320)
 - Type 3: Use the death endpoint form and identify the death with MI as the cause of death – then, go to the MI (on MI endpoint form) that goes with it (should have occurred within 24 hours of the death) and check CK-MB as adjudicated in Question 36 (CRF 320) is either < ULN or not done.
 - Type 4: (i) 4b = identify any positively adjudicated MI that occurred at a time of definite or probable stent thrombosis (ii) 4a – any MI that is PCI-related as per Q35 (making sure to not double-count with 4b).
 - Type 5: pick MIs that are CABG related (Question 35).
 - An analysis of all cause death following MI will be explored in a Cox regression model. The event of MI will be used as a time-dependent variable with treatment, interaction between treatment and the time dependent covariate of MI, stratification variable and the following fixed covariates: age as a continuous variable, NSTEMI vs. UA, diabetes (yes/no) and CrCl (as a continuous measure calculated by Cockcroft-Gault formula). .
 - Additional analysis evaluating time from non-fatal events to subsequent events will be done as follows:
 - Time to CV death following a non-fatal MI (CEC adjudicated). The denominator will be all MIs without a CV death within 1 hour.
 - Time to CV death or second MI following non-fatal MI (CEC adjudicated).

- Time to investigator reported CV death following investigator reported non-fatal MI.
 - Time to investigator reported CV death or second MI following investigator reported non-fatal MI.
 - Time to investigator reported CV death following any investigator reported recurrent ischemia (i.e., anytime the recurrent ischemia endpoint form is filled out).
 - Time to investigator reported CV death/MI from periprocedural MI.
- All Stroke: For those strokes that have been positively adjudicated, a summary by treatment group will provide the following:
 - Type of stroke (hemorrhagic or ischemic)
- Stent thrombosis. For those ST that have been positively adjudicated as definite or probable, a summary by treatment group will provide the following.
 - Primary analysis of stent thrombosis will be time from randomization to occurrence of stent thrombosis for all stents (whether they are placed during the study or whether the patient enters the study with a stent in place). Additionally, a secondary analysis of stent thrombosis will be done for those patients entering the study with a stent in place. Analysis of time from randomization to stent thrombosis will be repeated separately by stent type (BMS only; DES only; at least one DES).
 - For those patients with stent thrombosis the following will be summarized: Vessel type, diameter, length, minimum stent diameter, IVUS guidance, maximum balloon inflation pressure, diameter of balloon, thrombosis at a bifurcation lesion (yes/no), use of overlapped stents.
- Stent thrombosis adjudicated as definite, probable or possible will also be compared between treatment groups in the following fashion:
 - Across all patients and as well as separately for those patients receiving bare metal stent or drug eluting stent.
 - Summary of those stent thrombosis events that occurred after the discontinuation of study drug, aspirin and open label thienopyridine (if study drug was discontinued and open label thienopyridine was given).
 - By median aspirin dose within 5 days of the reported stent thrombosis event
 - Within each of the 3 pre-specified clopidogrel strata and within UA and NSTEMI patients.
 - The mean diameter and length of stents for those stents involved in a stent thrombosis will be provided overall as well as by bare metal and drug eluting stents.

- By timing of the occurrence of the event from implantation to stent thrombosis broken down by <24 hours, 24 hours -30 days, >30 days to 1 year, and >1 year to 2 years. This analysis will be done for all stents as well as broken down by BMS and DES. This analysis will also be repeated within each of the 3 pre-specified clopidogrel strata and run separately for those stents placed prior to the study and those stents placed during the study.
- The following information will be summarized for those patients undergoing a PCI during the study.
 - Elective vs. urgent, access site, access site closure method, whether the intervention resulted in a complication, whether the intervention resulted in subsequent surgical procedure, anticoagulants received, IIb/IIIa received, whether a hematoma occurred at the access site, the number lesions treated.
 - The following information will also be summarized: vessel type, location of lesion, lesion type, lesion risk, lesion length, number of stents used, use of overlapped stents, bifurcation lesion, per-procedural angiographic findings, outcome, IVUS guidance used, intracoronary devices.
 - For those stents placed during the study, the following will be summarized: type of stent, stent length, stent diameter, max post stent balloon inflation pressure, diameter/length of balloon used for post stent dilation, IVUS guidance used.
- CABG information: summarize elective/urgent, vessels bypassed, did procedure require re-exploration for bleeding, transfusions.
- Summarize the following information for diagnostic cath information.
 - Type of procedure (left heart cath/right heart cath/coronary angiography), access site, LVEF, access site closure method, native coronary vessels with >50% diameter stenosis, other vessel types with >50% stenosis, stent thrombosis identified, hematoma at access site.

5.3. Handling of Dropouts or Missing Data

Patients who discontinue study drug for either personal or other reasons will remain in the study and will be followed to assess whether a primary outcome event has occurred unless the patient has revoked consent indicating that no further follow-up is to be done thus prohibiting the sponsor from obtaining any further information on endpoints. For all efficacy analyses, the intent to treat philosophy will be employed, i.e., the outcome is time to event regardless of whether the patient is still on study drug or not. For all safety analysis, the primary analyses will be based on treated patients and whether the safety event occurs during the “at risk” period. A subject will be considered “at risk” during the period from the administration of the first dose of study drug up through 7 days after permanent study drug discontinuation, or the subject’s

discontinuation visit, whichever is earlier. If the clinical database does not have a date that the patient signed the informed consent, the patient's data will not be included in any analyses.

5.4. Multicenter Studies

Due to the large number of investigators and many investigators having a small number of patients, no adjustments will be made for primary and secondary analyses for investigator effects. However, the effect of investigator region and the interaction between the region and treatment on the primary endpoint will be assessed in a subgroup analysis. The regions to be included in subgroup analyses are North America, Central/Eastern Europe, Western Europe/Scandinavia, Latin America, East Asia, India subcontinent, Mediterranean Basin and Rest of World. Individual countries that comprise these regions are listed below:

Central/Eastern Europe	Bulgaria, Croatia, Czech Republic, Hungary, Lithuania, Poland, Romania, Russia, Serbia, Slovakia, Ukraine
Western Europe/Scandinavia	Austria, Belgium, Denmark, Finland, France, Germany, Portugal, Italy, Ireland, Netherlands, Spain, Sweden, Switzerland, UK
Latin America	Argentina, Brazil, Chile, Columbia, Costa Rica, Mexico, Panama, Peru
East Asia	China, Malaysia, Philippines, Singapore, South Korea, Taiwan, Thailand
Indian Subcontinent	India
North America	US/Puerto Rico, Canada
Mediterranean Basin	Tunisia, Israel, Egypt, Malta, Turkey, Greece
Rest of World	Australia, New Zealand, South Africa

Data from US will be presented separately as well but still included in North America for the purposes of interaction testing. In addition, while data will be displayed separately for Mediterranean Basin and Rest of World, they will be pooled together for the purposes of interaction testing due to small sample sizes within those regions.

5.5. Multiple Comparisons/Multiplicity

Secondary efficacy endpoints will be assessed in the same fashion as the primary outcome measure. No adjustment for multiple testing will be done.

5.6. Subject Disposition

The primary reasons for discontinuation will be summarized by treatment group and within each age cohort. The percent of subjects discontinuing study drug treatment, withdrawing from the study from each treatment group, and lost to follow-up will be compared using Pearson's chi-square test of homogeneity. The summary will be structured as follows:

Number of patients randomized

- #1. Study completed.
 - On study drug at time of completion.
 - Alive
 - Dead
 - Off study drug at time of completion (early discontinuation of study drug)
 - Alive
 - Dead
- #2. Study not completed (Note that these are 3 ways of breaking down information of those not completing the study. Each of the subcategories below will sum up number of patients not completing study.)
 - Study drug status
 - On study drug at time of discontinuation
 - Study drug discontinuation before study discontinuation
 - Reasons for study discontinuation
 - Subject decision
 - Sponsor decision
 - Physician decision
 - Vital status at study end
 - Known to be alive
 - Known to be dead
 - Unknown
- #3. Impossible to locate subject at database lock
 - Known to be alive
 - Known to be dead
 - Unknown

A separate table will summarize the reasons for permanent study drug discontinuation. Treatment groups will be compared with Pearson's chi-square test of homogeneity. Reasons are as follows:

- Subject had a procedure
- Adverse event

- Hemorrhagic
- Non-hemorrhagic
 - Need for oral anticoagulation
 - Investigator decision
 - Subject decision
 - Study drug unblinded
 - Lost to follow-up
- Vital status CRF (alive/dead)

Kaplan Meier curves along with log-rank test statistics will be provided for premature study drug discontinuation for any reason, premature study drug discontinuation due to an adverse event, and premature study drug discontinuation due to a hemorrhagic adverse event. In addition to the standard Kaplan Meier method, a cumulative incidence method (Gooley et. al. 1999) will also be implemented since it accounts for competing risks in estimating nonfatal event rates. It will be implemented via the SAS macro %cumincid.

5.7. Subject Characteristics

Subject characteristics will be obtained at baseline and will be summarized by treatment group. The summaries will include descriptive statistics (sample size, mean, standard deviation, minimum, median, and maximum) for the continuous variables and frequencies and percentages for the categorical variables. Subject characteristics on a continuous scale at baseline will be compared using analysis of variance (ANOVA) methodology. Subject characteristics on a categorical scale at baseline will be compared using Pearson's chi-square test of homogeneity. All characteristics will be summarized for 3 cohorts of interest: <75 years of age, all patients, ≥75 years of age.

The following baseline characteristics will be summarized and compared between the two treatment groups:

Demographics:

- age (as a continuous variable),
- sex,
- ethnic origin,
- geographic region as defined above in section 5.4,
- weight (continuous and as categorical <60, ≥60 kg)
- BMI (kg/m^2) (as continuous and categorical [<18.5 , 18.5 to <25 , 25 to <30 , ≥ 30]),
- Tobacco use at randomization will be described by these 6 mutually exclusive categories:

1. Never used tobacco prior to randomization
 2. Did not use tobacco in 30 days prior to randomization but used previously
 3. Used cigarettes < 10 cigarettes per day within 30 days of randomization, regardless of the use of other tobacco related products
 4. Used 10-20 cigarettes per day within 30 days of randomization, regardless of the use of other tobacco related products
 5. Used more than 20 cigarettes per day within 30 days of randomization, regardless of the use of other tobacco related products
 6. None of above, i.e., use of tobacco related products within 30 days of randomization but not cigarettes.
- Frailty characteristics for those >65 years. Percent of patients with at least 3 of 5 characteristics listed will be summarized.
 - In addition, the percent of patients experiencing each frailty characteristic will also be summarized:
 - Unintentional weight loss
 - Developed decreased grip strength
 - Developed increased fatigue/lethargy or declining endurance
 - Walks a distance of 5 m at a slower pace
 - Decline in typical physical activity level
 - 65 years old but none of the above checked

Medical history

- Commercial clopidogrel status: summarize % in each of the 3 strata
- Enrichment criteria:
 - Diabetes
 - Insulin
 - Non-insulin
 - Oral
 - Dietary only
 - Not treated
 - Not diabetic
 - Prior MI
 - Age ≥60 years

- Coronary revascularization (either PCI or CABG) at least 30 days before the onset of the index ACS event.
- Number of enrichment criteria met:
 - Patients who met 1 enrichment criteria
 - Patients who met 2 enrichment criteria
 - Patients who met 3 enrichment criteria
 - Patients who met all 4 enrichment criteria
- Family history of CAD
- Hypertension (yes/no)
- Hyperlipidemia (yes/no)
- PAD (yes/no)
- Prior history TIA (yes/no)
- Prior Ischemic Stroke (Note that we should not have any of these since it is an exclusion criteria- however we will tabulate any that may have randomized in error.)
- Other manifestation of cerebrovascular disease (yes/no)
- Documentation of coronary stenosis greater than or equal to 50% prior to presentation for evaluation of the index event (yes/no)
- Chronic Heart Failure (yes/no)
- Atrial Fibrillation (yes past, yes current, no); Summary of detailed questions from form 70 will also be given.
- Chronic renal insufficiency (yes/no), summary of 4 questions from form 80
- Peptic Ulcer Disease (yes/no)
- Lower extremity amputation to treat PAD (yes/no)
- Revascularization of iliac or femoral artery (yes/no)
- Carotid artery revascularization procedure (yes/no)
- Prior PCI (at any time yes/no)
- Prior Coronary Stent placed prior to randomization (yes/no)
- Prior CABG (at any time yes/no)
- GRACE risk score at admission- reported as a continuous variable (See appendix 2 for calculation)
- Baseline creatinine clearance (Cockcroft-Gault formula): <30, 30-60, ≥60

Index event

- Proportion patients with NSTEMI vs. UA
- Summarize timing of events as follows. This is to be done for all patients, and within each of the 3 stratum. Use time as a continuous variable (provide mean, SD etc.), and also as a categorical variable defined as less than 24 hours, 24-72 hours, 72 hours -5 days, 6-10 days (these categories may not be applicable for all time intervals below).
 - Time from symptom onset to first study drug dose
 - Time from symptom onset to first medical contact
 - Time from first medical contact to first dose of study drug.
 - Time from first medical contact to first commercial clopidogrel dose (strata 2 only)
 - Time from first commercial clopidogrel dose to time of first dose of study drug (strata 2 only)
- Killip class at time of Index event
- Medication at randomization
 - Lipid lowering agents e.g., statins type (none, all statin, atorvarstatin, other statin)
 - PPIs, overall and by specific type (note: more detail on PPIs follows in subgroup section)
 - H2 Blocker
 - PPI or H2 Blocker
 - Calcium channel blockers
 - ACE inhibitors or ARBs
 - Beta blockers.
 - Nitrates
 - Ranolazine
- Medication at entry
 - Anticoagulant for index event
 - GP IIb/IIIa use for index event
 - Received aspirin within 7 days prior to randomization (yes/no)
 - By Dose

- Time from symptom onset, first medical contact and from randomization to first aspirin dose will be summarized overall and within each of the 3 strata.
- Summary of peak cardiac CK, CK-MB, troponin.
- Where did subject present for index event? (ER vs. already hospitalized)
- Findings on ECG: New ST depression, New transient ST segment elevation, LBBB, RBBB, New T wave inversion, Paced rhythm
- Coronary angiography performed? (For No, summarize reason for no)
 - Was stenosis $\geq 30\%$ found in at least 1 major artery? [If “yes”, then summary of reasons revascularization was not performed will be provided]
- From diagnostic cath CRF: % patients with stenosis $> 50\%$, % patients with stenosis 30-50%.
- Was the LVEF assessed by echocardiographic imaging?
- Was the LVEF assessed by nuclear imaging?
- Initial creatinine result.
- Summary of patients randomized under original protocol and amendment B.
- Summary of patients started on old formulation, started on old and switched, and only administered new formulation.

Subject Characteristics by Region: In addition to the characteristics above being summarized across all randomized patients, the following information will be displayed by each pre-specified region:

- Number of countries in each region
- Number of patients enrolled in each region
 - Overall and stratified by age groups
- Median number of patients enrolled by each site in each region
- Median time in days from hospital admission to randomization
- Key patient baseline characteristics:
 - Percentage of male and female patients
 - Percentage of patients with each of the enrichment criteria
 - Median GRACE score: overall and for both age groups
- Distribution of patients by pre-specified clopidogrel strata at randomization
- Percentage of patients undergoing angiography before randomization
 - Percentage with obstructive (at least one lesion $> 50\%$) vs. non-obstructive disease (all lesions $> 30\%$ but $\leq 50\%$ on angiography).
- Answers to qualitative questions on contraindications to angiography (for patients who don't undergo angiography before randomization) from the CRF
- Answers to qualitative questions on contraindications for revascularization from the CRF

5.8. Treatment Compliance

Treatment compliance will be defined by the following treatment compliance ratio: the number of maintenance doses taken by the subject divided by the number of doses assigned. Compliance is defined as taking between 80% to 120% of the study drug dosage prescribed. Rates of compliance will be compared between treatment groups at each visit using Pearson's chi-square test. An overall rate of compliance will be compared between treatment groups as well (across all visits where the patient is still being administered drug, i.e., dropping those patients who have withdrawn consent or lost to follow-up).

5.9. Concomitant Therapy

Prior and concomitant medications will be summarized by treatment group. Concomitant medications will be compared between treatment groups by those given in hospital and those post discharge.

The effect of concomitant medications on the primary efficacy endpoint will be assessed using the Cox proportional hazard model (see subgroup analyses section below). Analyses will include, but not be limited to, the effect of 3-hydroxy-3-methylglutaryl coenzyme A (HMG Co-A) reductase inhibitors (statins), angiotensin converting enzyme inhibitors (ACEI), beta blockers, angiotensin receptor blockers (ARB), PPI, H2 blockers and the dose of aspirin (see section 5.11). Corresponding 95% confidence intervals for the hazard ratios will be provided.

5.10. Safety Analysis

5.10.1. Safety Endpoint Analyses

Time to first occurrence of GUSTO and TIMI defined bleeds (as defined in protocol Section 6.3.1) will be compared between treatment groups with stratified log-rank test similar to the methodology for the primary efficacy outcome. Classification of suspected bleeding events by the GUSTO criteria is determined by a programmed algorithm with review of selected cases by the adjudication committee as detailed below. Classification of suspected bleeding events by the TIMI criteria is determined by the adjudication committee. Corresponding 95% confidence interval for the hazard ratio of prasugrel versus clopidogrel will be constructed. The primary analysis of bleeding events will be for those events occurring during the "at risk" time period as defined in Section 5.1 above. A sensitivity analysis will consist of all events, regardless of their timing. Analyses of bleeds and other safety outcomes will be done for <75 year old subjects, all subjects, and the ≥ 75 year old subjects alone.

Analyses will be done for the following types of bleeds:

- Non-CABG related GUSTO severe or life-threatening bleeding

GUSTO severe/life threatening bleeding will be determined by the programmed algorithm and in some cases by the adjudication committee as described below. A bleed meets severe/life threatening if a patient has any of the following criteria:

- fatal bleed,

- intracranial bleed
 - bleed that results in hypotension (hemodynamic compromise) that required treatment with intravenous inotropic agents and/or treatment with a surgical procedure.
 - Based upon the construction of the CRF, those bleeds in which the investigator checked the CRF field "required surgical treatment" but did not meet any of the other three aforementioned criteria (fatal bleed, intracranial bleed, or bleed that resulted in hypotension) will be considered as a possible GUSTO severe/life threatening bleed. For these possible GUSTO severe/life threatening bleeds (i.e., those "requiring surgical treatment" but no other criteria were checked on the respective CRF fields), the adjudication committee will review the case and determine which of the 3 GUSTO criteria the bleed met: Severe/life threatening, moderate, or mild.
- Non-CABG related GUSTO severe, life-threatening, or moderate bleeding
 - GUSTO moderate bleeding is any bleed that resulted in the need for a transfusion that is not considered a GUSTO severe/life threatening bleed.
- Non-CABG related GUSTO severe, life-threatening, moderate or mild bleeding
 - GUSTO mild bleeding is any other bleeding event that does not require transfusion or cause hemodynamic compromise
- All GUSTO severe or life-threatening bleeds (CABG and non-CABG bleeds)
- Non-CABG related TIMI fatal bleeding
- Non-CABG related TIMI life-threatening bleeding
- Non-CABG related TIMI major bleeding
- Non-CABG related TIMI major or minor bleeding
- Non-CABG related TIMI major, minor or minimal bleeding

- ISTH definition of bleeding (Schulman et. al., 2005). This is a bleed that fits any of the following criteria:
 - fatal bleeding, or
 - bleeding in one of the following critical areas or organs: intracranial (taken as either a subdural hematoma on bleed adjudication form or as a hemorrhagic stroke), intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, [Note that intraspinal, intraarticular compartment syndrome will be obtained from a search on the “other” field in the bleeding adjudication form.] and/or
 - bleeding causing a fall in hemoglobin level at least 2g/dL or leading to transfusion of 2 or more units of whole blood or red cells.

Within each of the TIMI and GUSTO bleeding types listed above, the following will be summarized and compared between treatment groups:

- Provocation of bleed: procedure-related , spontaneous, trauma
- Whether the bleed required: hospitalization (or prolongation), intravenous intotropic agents, laboratory evaluation, medical treatment, surgical treatment or a transfusion
- Location of bleed (as adjudicated)

NOTE: Hemorrhagic strokes will be counted as a bleeding event. These events are recorded on stroke CRF but will be counted as a bleeding event based upon the specifications of the respective bleeding classification scales.

Number needed to harm (NNH) will be provided using Kaplan-Meier estimates at 12 and 24 months for GUSTO severe or life-threatening bleeds and for TIMI major bleeds.

An analysis of all cause death following a GUSTO severe or life-threatening bleed will also be performed. This will be done in a Cox regression model with the event of bleed as a time-dependent covariate with treatment, the interaction between treatment and the time dependent covariate of bleed and the following fixed covariates: age, NSTEMI vs. UA, diabetes (yes/no) and CrCl (as a continuous measure calculated by Cockcroft-Gault formula). Remaining on study drug will also be a time dependent variable in the model, i.e., it is possible that a patient has a bleed, then discontinues study drug and then has an ischemic event that leads to death. In order to accommodate this, a time dependent covariate will be added that is equal to 1 when the patient is on the drug and 0 when the patient discontinues study drug. An additional model will only consider those deaths after 30 days of the bleed, i.e., to evaluate the long-term effect of a major bleed.

CABG-related bleeds will also be summarized. CABG-related TIMI major and CABG-related TIMI major or minor bleeds will be summarized and compared between treatment groups. In addition, summary statistics and comparison between groups will be done as to whether the CABG bleed was fatal, whether it was associated with an urgent or elective procedure, whether a transfusion was required and the timing between the most recent dose of study drug to the

CABG. Transfusions will also be summarized: Patients who received any transfusion during the study, summary of type of transfusion.

5.10.2. Adverse Event and Laboratory Analyses

As mentioned in Section 5.1, primary analysis of adverse events and laboratory measurements is for those patients in the “at risk” set, i.e., treated patients still on study drug or within 7 days of coming off. Adverse events will be summarized as treatment-emergent adverse events (TEAEs). Treatment-emergent adverse events are defined as events that first occurred or worsened after baseline. Rates of TEAEs will be presented for each treatment group and between-group comparisons will be performed using a chi-square test. Summary tables will include all those TEAEs that were reported in $\geq 1\%$ of the total study population by System Organ Class and Preferred Term (decreasing frequency in the prasugrel group). In reporting TEAEs, the events will be divided in events that are hemorrhagic and those that are non-hemorrhagic. A report will also be generated that lists any TEAE that occurred and are significantly different between the two treatment groups ($p < 0.05$) in any of the three cohorts of patients. This report will show the analyses for < 75 , ≥ 75 years and all patients.

Similar to the reports for TEAEs, reports will be generated for those adverse events that are deemed as serious, that are reported with SAEs occurring in $\geq 1\%$ of the total study population, and that are reported to have occurred significantly different between treatment groups. Additionally, TEAEs (by hemorrhagic and non-hemorrhagic), SAEs and discontinuations due to AE will be shown for the following age cuts: < 65 , 65-74, 75-84 and 85 and over.

Change from baseline to endpoint (last available observation during the at risk period) will be compared between treatment groups for central laboratory measurements (for example, chemistry and hematology measures) using an ANOVA with treatment, commercial clopidogrel status and baseline value in the statistical model. The incidence of treatment-emergent abnormal laboratory values (defined as a change from normal at baseline to abnormal at endpoint based on central lab ranges) will be tabulated by treatment group and compared between groups using a chi-square test.

Discontinuation due to an adverse event will be summarized by preferred term and compared between treatment groups. A listing of discontinuations due to adverse events or death will be provided.

Blood pressure will be summarized at each visit for each treatment group. To compare the treatment groups, a likelihood-based mixed-effects repeated measures analysis will be done with treatment, time, treatment by time interaction, and commercial clopidogrel status as a covariate for the < 75 year old analysis. This approach accounts for the bias caused by non-random missing data better than imputing missing values using a last observation carried forward approach. For the analysis of all patients, the age strata will also be included.

5.10.3. Neoplasm analyses

To compare the incidence at study-end of all new, non-benign neoplasms between study treatments in subjects with either (i) no baseline history of malignancy or (ii) malignancy with treatment judged to have been curative.

New non-benign neoplasms will be determined as follows:

- Adjudication form is marked as follows:
 - “Yes” malignancy was confirmed.
 - Confirmed malignancy was after randomization per the date of initial detection.
 - “No” to whether the confirmed malignancy was a recurrence.
- Population of interest, i.e., i) no baseline history of malignancy or (ii) malignancy with treatment judged to have been curative will be determined as follows:
 - Patients who answered “No” to the question of “is there a personal history of any malignancies.”
 - Patients who answered “Yes” to “personal history of malignancies” AND answered “No evidence of disease” for status at baseline.

This analysis will be based on population described above and on all cancers that meet the above criteria, including all skin cancers, using a log-rank test of time from first dose of study drug to date of initial clinical detection. The CEC will determine this date based on all available information and will record this date on the adjudication form.

Using the same method as described above, additional sensitivity analyses will be done as follows:

1. Repeat the analysis (new, non-benign neoplasm) but use all randomized patients as the denominator.
2. Compare rates for those cancers that were diagnosed > 30 days after randomization.
3. Exclude all skin cancers with the exception of melanoma.
4. Repeat analysis for those cancers which were adjudicated as detected from bleeding event. Denominator is everyone who had a GUSTO defined bleed (severe, moderate or mild).
5. Repeat analysis for those cancers which were adjudicated as detected from evaluation of anemia and evaluation of bleeding event or anemia.
6. Repeat analysis for those patients without a GUSTO defined bleed as denominator. Numerator is new non benign cancers.
7. Repeat analysis for all cancers for colorectal alone and all cancers excluding those adjudicated as colorectal.

8. Repeat analysis but use date of histological confirmed diagnosis as the start time of the cancer.
9. Cox regression model that includes the following risk factors:
 - personal history of any malignancies,
 - family history (of either colon or breast cancer),
 - current or past smoker,
 - regular alcohol use,
 - age,
 - gender,
 - geographic region
 - BMI over 30
 - Menopausal status/HRT – of course since this is compounded with sex, this would be used in an analysis of women only.

New non-benign neoplasms will be summarized by:

- location (as adjudicated)
- stage of malignancy (as adjudicated)
- method by which malignancy was initially detected (e.g., routine cancer screening, routine physical exam, bleeding event, diagnostic procedure) (as adjudicated)
- treatment of malignancy (as collected by investigator) initially given
- hospitalized for malignancy for reasons other than planned treatment (as collected by investigator)
- Metastatic during study

A comparison of treatment groups will be done on the death rate due to malignancy (adjudicated) and all cause death between treatment groups using Fisher's exact test for

- All patients diagnosed with new non-benign neoplasm.
- All randomized patients.
- All patients with pre-existing cancer.

A comparison between treatment groups will be done of status of disease as adjudicated at end of study by CEC. Denominator is all patients with new non-benign cancers, numerator are those with active disease.

Recurrent cancers:

- Summarize and compare rates of recurrent cancers (adjudicated as recurrent) between treatment groups. Denominator is patients with history of malignancy with no evidence of active disease or stable/inactive disease, numerator are those patients adjudicated as having “recurrent” disease.

5.11. Subgroup Analysis

Subgroup analyses, relative to primary efficacy and key safety endpoints (GUSTO life-threatening/severe bleeding and TIMI major/minor) will include analyses by the following subgroups. Additionally, subgroup analyses will be run for all cause death. Each variable will be analyzed individually with a model that contains the treatment, the subgroup variable, subgroup by treatment and stratification variable (commercial clopidogrel status) and age when analyzing the all patient cohort. The treatment-by-subgroup interaction tests will determine whether treatment differences are the same for each subgroup category. Summary results (i.e., n, N, %, HR with CI, KM estimates) will be displayed within each subgroup. These analyses will be done for each cohort: <75, all patients, ≥75 years.

5.11.1. Patient Characteristics

- Commercial clopidogrel status as defined in Appendix 1. This is our stratification variable; however, we need to test the interaction between this and treatment to evaluate whether there is a differential treatment effect between the 3 strata. This model will contain treatment, strata and strata by treatment interaction.
- Sex
- Age (<75 vs. ≥75 years): again this is our second stratification variable; however, we need to test whether the interaction is significant.
- Age defined by the following cuts: <65 vs ≥65, and 4 categories of <65, 65-74, 75-84, and 85 and over
- NSTEMI vs. UA
- GRACE score sub-group split by median score (GRACE scored as calculated by Eagle et. al. 2004. See appendix 2.)
- GRACE score by following predefined categories: <100, 100-140, >140
- Diagnostic coronary angiography vs. none (at admission)
- For those patients with diagnostic catheterization: Obstructive disease (≥50% stenosis) versus <50% stenosis

Geographic region: North America, Central/Eastern Europe, Western Europe/Scandinavia, Latin America, East Asia, Indian subcontinent, Mediterranean Basin, Rest of World. Note: US data will be presented separately but North America will be used for the interaction test. Also, Rest of World and Mediterranean Basin will be pooled for purposes of the interaction test.

- Weight(kg): $<60, \geq 60$
- BMI (kg/m^2): $<18.5, 18.5 \text{ to } <25, 25 \text{ to } <30, \geq 30$
- Tobacco use at time of randomization: 6 categories as defined by section 5.7. The treatment effect between category 1 and 2 will be tested in a model with treatment, tobacco category (only including 1 and 2), the interaction and the stratification variables. If the interaction is not significant ($p < 0.10$), then categories 1 and 2 will be pooled for this analysis. Similarly, a test will be done to compare treatment effect between categories 4 and 5. If the treatment effect is similar, then these two categories will be pooled.
- Cigarette and/or Tobacco use at time of randomization. Perform pair-wise comparison between the distinct categories as result from finding outlined in bullet above.
- Tobacco use at time of randomization. See section 5.7 for definition. For this subgroup analysis, category 1, 2 and 3 will be pooled against categories 4 and 5.
- Cigarette use at time of randomization. Categories 1 and 2 and 6 will be pooled compared to categories 3, 4 and 5.
- Peak baseline troponin levels for NSTEMI patients: 0-1, $>1 \text{ to } \leq 3 \times \text{ULN}$, $>3 \text{ to } \leq 5 \times \text{ULN}$, $> 5 \times \text{ULN}$
- All prasugrel patients who received 5 mg will also be analyzed and compared to clopidogrel patients with the same characteristics. That is, all patients who are ≥ 75 together pooled with those patients $<60 \text{ kg}$ will be compared between prasugrel and clopidogrel. The complement will also be evaluated, i.e., all patients who are <75 and ≥ 60 will be compared between prasugrel and clopidogrel.

5.11.2. Baseline history/conditions

- Family history of Coronary Artery Disease (yes/no)
- Diabetes (Yes treated with insulin, Yes treated without insulin, (subcategories of oral and diet only), Yes not treated, No.)
- Hypertension (yes/no)
- Hyperlipidemia (yes/no)
- Prior MI (yes/no)
- Prior stenosis of $\geq 50\%$ (yes/no)
- Chronic heart failure (yes/no)
- Atrial fibrillation (Yes Past, Yes Current, No)
- Chronic renal insufficiency (yes/no)
- PUD (yes/no)
- Has a coronary stent ever been implanted prior to randomization in trial (yes/no)

- Prior revascularization (PCI or CABG) (yes/no)
 - Prior PCI (yes/no)
 - Prior CABG (yes/no)
- Vascular disease in 1, 2 or 3 vascular beds (everyone has 1), 2 beds include either PAD or Cerebrovascular disease. PAD is defined as: PAD, amputation or prior revascularization of iliac or femoral artery. Cerebrovascular disease is defined as: other manifestation of cerebrovascular disease, stroke/TIA or carotid artery revascularization. 3 vascular beds includes PAD and Cerebrovascular disease. (categories will then be 1, 2 or 3). The following individual questions will be analyzed separately as well.
 - PAD (yes/no)
 - Did subject have lower extremity amputation to treat PAD (yes/no)
 - Did subject have prior revascularization of an iliac or femoral artery (yes/no)
 - Other manifestations of cerebrovascular disease (yes/no)
 - Has a carotid artery revascularization procedure been performed (yes/no)
- Creatinine clearance (Cockcroft-Gault formula): <30, 30-60, ≥60
- Frailty score

5.11.3. Medications

5.11.3.1. Medications used during index hospitalization

- GPIIb/IIIa (within index hosp)
 - By sex within GPIIb/IIIa use
 - By timing within GPIIb/IIIa use (administered prior to cath or same day or after cath)
- Anticoagulants (within index hosp)

5.11.3.2. Aspirin Use

- At randomization: doses <100, 100-250 and >250
- Median aspirin dose during study: median dose to be calculated 3 ways; including and not including the loading dose as well as median dose 5 days prior to event (or censoring). Treatment effect will be summarized within each of the 3 stratum as well as overall. Doses to be summarized: ≤100 mg, >100 - < 200 mg, > 200 - < 300 mg, > 300 mg),

5.11.3.3. Concomitant Medications at time of randomization

- Statin therapy (yes/no)

- ACE Inhibitor (yes/no)
- Beta Blockers (yes/no)
- Proton Pump Inhibitor (yes/no). Specific types of PPIs will also be analyzed individually. See additional analyses for PPIs below as well.
- H2 receptor antagonist (yes/no)
- Calcium channel blocker (yes/no)
- Diuretics (yes/no)
- Coronary vasodilators (yes/no)

5.11.3.4. Proton pump inhibitors (PPI)

In addition to the subgroup analysis mentioned above, analysis of PPI will be done in a Cox regression model with the use of PPI as a time dependent covariate, i.e., the flag will be set to 1 when a patient is taking a PPI, and then 0 if/when they go off the PPI. The outcome will be primary efficacy composite endpoint. Treatment and the interaction between treatment and the time dependent covariate of PPI use will also be included in the model along with the stratification variable. Additional covariates in the model will include UA vs. NSTEMI, age, diabetes (yes/no), and CrCl (as a continuous measure calculated by Cockcroft-Gault formula). If the treatment by PPI use term is significant, then PPI use will be evaluated within each treatment group separately. An additional analysis will be done for those patients that stayed on PPI the entire study period to those patients who never used a PPI. The same model as described above will be used- i.e., treatment, PPI use, treatment by PPI. strata with UA vs. NSTEMI, age, diabetes (yes/no), and CrCl (as a continuous measure calculated by Cockcroft-Gault formula) as covariates. In addition to analyzing all PPIs, this analysis will be repeated for specific PPI types.

5.12. Adjustments for Covariates

In addition to the model described in section 5.2.2 that uses age (as a continuous measure), NSTEMI vs. UA, diabetes yes/no and CrCl (as a continuous measure calculated by Cockcroft-Gault formula) as covariates, a stepwise Cox regression model will be done for the primary efficacy outcome and the key bleed outcomes (GUSTO life-threatening/severe bleeding and TIMI major/minor) with a larger selection of variables. Potential factors that will be included into the model are listed below:

- Treatment
- Commercial clopidogrel status (strata as described in Appendix 1)
- Sex
- Age (as continuous variable)
- NSTEMI vs. UA
- GRACE score (as continuous variable), see Appendix 2 for calculation
- Geographic region (as defined in section 5.4)
- Weight (as continuous variable)

- Tobacco use (current use at time of randomization: as a result of distinct categories as described in section 5.11.1)
- Diabetes (yes/no)
- Prior revascularization (yes/no either PCI or CABG)
- Creatinine Clearance (as a continuous variable)
- Prior MI (yes/no)
- Hypertension (yes/no)
- Atrial Fibrillation (Current vs. none or history)
- Coronary Heart Failure (yes/no)
- Vascular disease in 1, 2 or 3 vascular beds (as defined above in subgroup analyses)
- On aspirin at time of randomization
- Peak baseline troponin level

In addition to a stepwise Cox model, the interaction between the above variables and treatment will be explored in a separate model. The multivariate model will also be run for prasugrel alone.

An additional model will look at tobacco use using the definition with 6 categories as defined in section 5.7 in a step wise Cox model with the other factors listed above. In addition to the analysis above that includes the covariate of cigarette and/or tobacco use (current use at time of randomization), a sensitivity analysis will also be done using smoking status as a time-dependent variable. The time dependent smoking status is defined as the smoking status observed prior to event, or if no event, prior to the censored time. Interactions between tobacco use and other prognostic factors will also be explored such as age, diabetes, prior clopidogrel use, and UA vs. NSTEMI.

5.13. Platelet Function Substudy

Approximately 1/3 of the TRILOGY patients will have platelet function measures performed. At those sites choosing to participate in the substudy, all subjects will have their platelet function measured. Platelet aggregation (PA) will be measured by the Accumetrics VerifyNow® P2Y12. Measurements will occur prior to first administration of study drug, 2 hours post study drug administration, 30 days, 3 months, 6 months and every following 6 months as long as the patient is in the study and remains on study drug. If a subject experiences an efficacy endpoint event or a bleeding event, an attempt is made to obtain an additional blood sample for platelet function measures. Inhibition of platelet aggregation will be computed by the Accumetrics VerifyNow® P2Y12 assay from 2 measures: P2Y12 Reaction Units (“PRU”) is an estimate of P2Y12 receptor-mediated platelet aggregation (rate and extent) in response to ADP in the ADP/PGE1 channel. “BASE” is an independent measurement based on the rate and extent of platelet aggregation in the Thrombin Receptor Activating Peptide (TRAP) channel. The device reported % inhibition is the percent difference between the "PRU" and "BASE" values on any given occasion. The “BASE” value serves as an estimate of the subject’s baseline platelet function independent of P2Y12 receptor inhibition. Percent inhibition, as reported by the Accumetrics VerifyNow P2Y12 device, is calculated from PRU and BASE values as follows: % Inhibition = $(1 - \text{PRU}/\text{Base}) \times 100$.

All analyses to evaluate relationship between clinical outcome and platelet aggregation (PA) with clinical efficacy or safety endpoint as outcome variable will be conducted using all CEC adjudicated events in all randomized subjects, and the analysis may also be repeated using the CEC adjudicated events while at risk in all treated subjects. For all analyses to explore treatment effect on PA with PA as the outcome variable will be performed in all treated subjects. Where noted, the stratification variables of prior clopidogrel use and age (<75 / ≥ 75) will be included as covariates in the models

Values from the Accumetrics VerifyNow® P2Y12 assay that meet the following criteria will be **removed** from all analyses:

- Measurement was within 7 days of receiving a GP IIb/IIIa inhibitor.
- The sample was assayed outside the acceptable window (10 minutes to 4 hours after sample collection) based on difference between collection time and time assay was run.
- Device reported percent inhibition as greater than 100%
- BASE or PRU value greater than 500
- BASE values less than 100

5.13.1. Platelet Aggregation Baseline Characteristics

Baseline characteristics and medical history will be presented for those patients in the platelet aggregation study and those not in this substudy. Characteristics of those in the substudy (across treatment groups) will be compared to those not in the substudy to verify that the patients in the substudy are a reasonable representation of the study of the whole. . In addition, baseline characteristics and medical history will also be compared between treatment groups within the substudy.

5.13.2. Platelet Aggregation as Predictor of Outcome

To test the hypothesis that a lower risk of the composite endpoint will be seen for those subjects with lower levels of platelet aggregation (PA), a Cox regression model will be performed with PA level as a time-dependent covariate in the model. In addition, the stratification variable of commercial clopidogrel status will be included in the model. When analyzing all subjects, the additional strata variable of age (<75 versus ≥ 75 years) will also be included. Platelet aggregation will be used as a continuous measure in the model. This initial model will not include treatment, since the hypothesis of interest is whether platelet aggregation predicts clinical outcome, regardless of study drug treatment. Additional models will evaluate covariates (in addition to PA) such as treatment group, gender, co-morbid conditions, etc.

A separate Cox regression will also be conducted using only the 30-day post-study drug dose PA measurement in the model to test whether a PA measurement obtained shortly after randomization is predictive of subsequent event-free survival. The stratification variable of commercial clopidogrel status will be included in this model along with age strata. Note that since this analysis will be based on the 30 day PA measurement, only those events occurring after 30 days will be included. The analysis described above will also be repeated using only the 2 hour post-dose PA. In addition, the last PA will be analyzed as a dichotomous variable by

using poor responder cutoff values of 230, 208 and 170 respectively. This analysis will be done using the initial cox regression model described above. Lastly, the PA will be analyzed by quartiles, that is, the data will be divided into 4 equal groups (based on last available PA measurement prior to event) with event rates compared between quartiles using Cochrane-Armitage trend test.

5.13.3. Comparison of treatment groups of PA

Platelet aggregation (PA) measured at 2 hours, 30 days, and most recently obtained prior to censoring will be compared between treatment groups using separate ANOVAs with treatment, the stratification variables, and baseline PA in the model. This analysis will also be repeated including only stratum 2 and 3.

In addition, the mean PA will be compared between treatment groups across the entire maintenance phase (30 days and subsequent measurements) of the study within a likelihood-based mixed-effects model repeated measures analysis. This approach accounts for the bias caused by non-random missing data better than imputing missing values using a last observation carried forward approach. This will be performed using PROC MIXED in SAS with the following effects in the model: treatment, visit, visit by treatment interaction, baseline PA and the stratification variables in the model as fixed effects. The variance-covariance structure for the repeated measures will be fit with either a compound symmetry or auto-regressive [AR(1)] fit. The choice of models between CS and AR(1) will be evaluated by using the AIC fit statistic (smaller is better). The treatment main effect test will test whether the overall mean PA differs between treatment groups across the entire maintenance phase. In addition, contrasts will be set up within the repeated measures model to test whether treatments differ at each of the visits. This mixed-effects model repeated measures analysis of the platelet aggregation measurements will also be utilized to estimate intrasubject and intersubject variability for prasugrel and clopidogrel. Intrasubject and intersubject variability will be compared between the prasugrel and clopidogrel treatment groups. Estimates of the different variance components will be output from SAS and tested between treatment groups using a Wald test.

The analysis above, i.e., comparing PA values over time, will also be done by dose group. Thus, all patients on 10mg of prasugrel will be compared to those clopidogrel patients with the same characteristics (i.e., under 75 years of age and over 60kg) while the 5 mg of prasugrel will be compared to clopidogrel patients with the same characteristics (over 75 or under 60kg).

5.13.4. Subgroup analysis of PA for those patients previously treated with Clopidogrel

For those subjects who entered the study on clopidogrel (chronic use), a Cox regression will be done for the primary composite outcome with randomized treatment, baseline PA (measured prior to receiving first dose of study drug), the stratification variables and the interaction between baseline PA and randomized treatment. The interaction test will test the hypothesis that the difference between treatment groups is dependent on the PA produced by clopidogrel. For example, if a subject achieves a high % inhibition on clopidogrel prior to randomization, the

difference in survival between treatment groups would be smaller than for those subjects who obtain a low level of % inhibition on clopidogrel prior to randomization. It is hypothesized that for the latter subjects, the difference between treatment groups would be the greatest. For different baseline levels of PA, descriptive statistics will be given for primary efficacy outcome for prasugrel vs. clopidogrel including HRs, CIs etc.

5.13.5. Bleeding and PA

Similar analyses as described for composite endpoint above will be done for bleeding outcomes. The outcomes analyzed will be first occurrence of a GUSTO severe or life-threatening bleed, GUSTO severe/life threatening or moderate and for a TIMI major or minor bleed.

5.13.6. ROC Analysis

An ROC curve will be plotted for PRU and % inhibition for both the primary efficacy outcome measures as well as a bleeding measure (TIMI Non-CABG related major or minor bleeding, GUSTO moderate/severe bleeding). This analysis is done irrespective of study treatment. This will enable us to assess the predictive ability of platelet aggregation on efficacy and bleeding. An ROC curve is the plot of sensitivity versus (1-specificity) where different points on the curve correspond to different cutpoints. If the area under the curve=1, then the test is perfectly accurate in predicting the outcome of interest. If the area is ~0.5 (or the confidence interval for the area includes 0.5) then the predictive ability of the measurement is no better than random chance. This will be done in PROC LOGISTIC procedure of SAS where the c-statistic is the nonparametric estimate of area under the curve. This statistic will be provided with 95% confidence intervals. The optimal cutoff for PRU and % inhibition will be determined by smallest difference between the ROC curve and the upper left hand corner of the graph. This will be done for PRU and % inhibition for the measure most recently obtained prior to censoring (or last one collected prior to an event). The predictive ability of PRU and % inhibition can also be compared by testing the difference between area under the curves.

5.13.7. Multivariate Predictive Model

As defined above in section 5.12, a multivariate stepwise Cox regression model will be done for the primary efficacy measure and bleeding outcomes. This model will also be constructed for the platelet sub-study patients. Once the model is completed, PRU (and % inhibition) will then be added to the model to obtain adjusted hazard ratio for PRU (and % inhibition) and its significance.

5.13.8. Poor Responder Analysis

The proportion of patients with PRU>230 will be compared between the treatment using Pearson chi-square test in each age cohort and CMH test in the overall group with adjustment on age cohort. This will be done for the 30 day PRU value, 18 month PRU as well as the most recently value obtained prior to censoring (or prior to an event) for each patient. This will be repeated using the cutoffs of 208 and 170. When analyzing percent inhibition, this will be done using 15%.

5.13.9. Comparison of Prasugrel Formulations

The two prasugrel formulations will be compared using a repeated measures model. This model will use all available platelet measurements collected over time. The two formulations will be compared between those subjects that were only given the old formulation to those only given the new formulation to those patients starting on the new formulation and switched over.

5.13.10. Subgroup Analyses

PRU and % inhibition will be compared over time with a repeated measures model testing for a difference between subgroups of interest. All available measures will be included in this repeated measures model. The model will include subgroup, treatment, visit, subgroup by treatment interaction, baseline PA and the stratification variables in the model as fixed effects. In addition, to evaluate whether PRU predicts efficacy outcomes differentially between subgroups, a Cox proportional hazards model will be done with the primary efficacy variable as the outcome and treatment, subgroup, stratification variables, PA and PA by subgroup interaction as the predictors. This will be done for PRU and % inhibition for the measure most recently obtained prior to censoring (or last one collected prior to an event). These analyses (both the repeated measures analysis and the Cox model) will be done for the following subgroups: gender, weight (<60kg, ≥60kg), PPI use (yes/no as prescribed at discharge), aspirin dose (using 3 levels: ≤100, >100-250, >250), ethnicity (Caucasian, Asian, other), tobacco use (current use at time of randomization per distinct categories described in section 5.11.1), diabetics (yes/no), renal insufficiency (as by CrCl cut at 60), age (<75, ≥75- note that this variable will be in all the models already, but we will test for interaction in this additional model).

5.13.11. Biomarker Measurements

The biomarkers of inflammation (high-sensitivity C-reactive protein [hsCRP]) and hemodynamic stress (N-terminal prohormone brain natriuretic peptide [NT-proBNP] or brain natriuretic peptide [BNP]) will be collected on all platelet function substudy patients at baseline, day 30, month 6 and end of study. In general, analyses described for PRU and % inhibition will be repeated for these 2 measures as well. For example: predictive ability of CRP and proBNP on efficacy as described above in 5.13.2 and comparison of measures between treatment groups over time. A log-transformation may be used due to the possibility of the distribution being skewed. Additionally quartiles of proBNP may be used in the model. Multivariate analyses as well as ROC curves will be explored as well. The relationship between PRU and % inhibition to biomarkers may be explored via regression analyses and correlation coefficients. Multivariate models with both CRP, BNP and PRU as predictive measures of the primary efficacy outcome will also be explored.

5.13.12. Aspirin Assay

The value of the aspirin assay collected at both day 1 and day 30, will be used in a Cox proportional hazards testing to see whether it is a significant predictor of primary efficacy outcome using the same model as described for the P2Y12 assay in 5.13.2. In addition, a categorical analysis will be used for the aspirin assay, comparing the proportion of “responders” using the cutoff of >550.

5.13.13. *Aspirin assay combined with PRU*

The Day 30 measurements of the aspirin assay (yes/no response cut at 550) and the P2Y12 assay (yes/no response cut at 230) will be combined in a predictive model for the primary efficacy outcome. Both variables (aspirin yes/no, PRU yes/no) will be included in the model along with an interaction between the two variables.

5.14. Genomics Substudy

A separate SAP has been written for the genomics analyses.

6. References

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7. Appendices

Appendix 1. Study Drug Treatment by Commercial Clopidogrel Status

Table TABY.1. Study Drug Treatment by Commercial Clopidogrel Status

Medically Managed UA/NSTEMI Subjects	
Commercial Clopidogrel Status at Time of Randomization	Randomized Treatment
Stratum 1 Either clopidogrel-naïve or not at steady state ^a on commercial clopidogrel, with a decision for medical management and randomization within 72 hours following onset of the index event.	<u>Loading Dose/Maintenance Dose:</u> Clopidogrel 300- mg loading dose followed by 75-mg once-daily maintenance dose <u>or</u> prasugrel 30-mg loading dose followed by 5 / 10- mg once-daily maintenance dose ^b (each administered on a background of low-dose aspirin).
Stratum 2 Commercial clopidogrel loading dose of at least 300 mg administered within 72 hours following onset of the UA/NSTEMI index event with administration of daily maintenance dose thereafter.	<u>Maintenance Dose Only:</u> Clopidogrel 75-mg once-daily maintenance dose <u>or</u> prasugrel 5 / 10-mg once-daily maintenance dose ^b (each administered on a background of low-dose aspirin).
Stratum 3 Commercial clopidogrel treatment prior to the index event and the subject deemed to be at steady state at the time of the onset of the index event; and MD maintained up until time of randomization.	
^a Subjects defined as clopidogrel-naïve or not at steady state are those subjects who: (i) have received a maintenance dose of commercial clopidogrel for <5 consecutive days immediately prior to the index event, AND (ii) have NOT received a commercial clopidogrel loading dose within 72 hours following the onset of the index event.	
^b Subjects ≥75 years of age or <60 kilograms of body weight will receive the 5-mg maintenance dose.	

Appendix 2. Calculation of the GRACE score

Calculation of the GRACE score

Risk Calculator for 6-Month Postdischarge Mortality After Hospitalization for Acute Coronary Syndrome		
<p>Record the points for each variable at the bottom left and sum the points to calculate the total risk score. Find the total score on the x-axis of the nomogram plot. The corresponding probability on the y-axis is the estimated probability of all-cause mortality from hospital discharge to 6 months.</p>		
Medical History	Findings at Initial Hospital Presentation	Findings During Hospitalization
<p>① Age in Years Points</p> <p>≤29 0</p> <p>30–39 0</p> <p>40–49 18</p> <p>50–59 36</p> <p>60–69 55</p> <p>70–79 73</p> <p>80–89 91</p> <p>≥90 100</p> <p>② History of Congestive Heart Failure 24</p> <p>③ History of Myocardial Infarction 12</p>	<p>④ Resting Heart Rate, beats/min Points</p> <p>≤49.9 0</p> <p>50–69.9 3</p> <p>70–89.9 9</p> <p>90–109.9 14</p> <p>110–149.9 23</p> <p>150–199.9 35</p> <p>≥200 43</p> <p>⑤ Systolic Blood Pressure, mm Hg</p> <p>≤79.9 24</p> <p>80–99.9 22</p> <p>100–119.9 18</p> <p>120–139.9 14</p> <p>140–159.9 10</p> <p>160–199.9 4</p> <p>≥200 0</p> <p>⑥ ST-Segment Depression 11</p>	<p>⑦ Initial Serum Creatinine, mg/dL Points</p> <p>0–0.39 1</p> <p>0.4–0.79 3</p> <p>0.8–1.19 5</p> <p>1.2–1.59 7</p> <p>1.6–1.99 9</p> <p>2–3.99 15</p> <p>≥4 20</p> <p>⑧ Elevated Cardiac Enzymes 15</p> <p>⑨ No In-Hospital Percutaneous Coronary Intervention 14</p>
<p>Points</p> <p>① _____</p> <p>② _____</p> <p>③ _____</p> <p>④ _____</p> <p>⑤ _____</p> <p>⑥ _____</p> <p>⑦ _____</p> <p>⑧ _____</p> <p>⑨ _____</p> <p>Total Risk Score _____ (Sum of Points)</p> <p>Mortality Risk _____ (From Plot)</p>		
<p>Predicted All-Cause Mortality From Hospital Discharge to 6 Months</p> <p>Probability</p> <p>Total Risk Score</p>		

Screening Log (Screen) *(form title/tab name)***Screening Log** *(section title)*

*****NOTE: In order to create a subject casebook, the SCREEN and ENROLL forms must be completed. After submitting this form, please complete the ENROLL page for the subject and submit immediately.*****

	Initials [<i>hidden</i>] (<i>R</i>)	(A3)
1.	Date of birth (<i>R</i>)	(1900-2002, Y)

Enrollment (Enroll) *(form title/tab name)***System Enrollment** *(section title)*

*****NOTE: This form must be completed immediately after the system SCREEN form in order to create a subject casebook for TRILOGY.*****

1.	Subject number <i>(R)</i>	(A11)
2.	Generate an electronic case report form for this subject? <i>(R)</i>	1 Yes 0 No

Date of Visit (DOV) *(form title/tab name)***Date of Visit** *(section title)*

1.	Date of visit <i>(R)</i>	/	/	(2008-2020,DMY)
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Type of Visit *(section title)*

2.	What type of visit was performed? <i>(R)</i>	4	Onsite visit
		12	Telephone visit with subject
		95	No contact (onsite or telephone) with the subject

Demographics (Demog) (form title/tab name)

Demographics (section title)

1.	Date of birth (R)	(1900-2002, Y) [mapped from screen]		
2.	Subject's age at randomization (R, SV)	(N3)		
	Cohort (hidden) (NR)	(A1)		
3.	Sex (R)	1	Female	
		2	Male [mapped from IVR, read only]	
4.	Ethnic Origin (R)	1	Caucasian	
		2	African	
		3	Hispanic	
		4	Native American	
		5	East Asian	
		6	West Asian	
		44	Aboriginal	
		47	Maori	
5.	Subject number (R)	(A11) [mapped from enroll]		
	Initials (hidden) (NR)	(A3)		

Height and Weight (section title)

6.	Height (R)	1	(N5.0)	centimeters	inches
		93	Not done		
7.	Weight (R, SV)	1	(N5.0)	kilograms	pounds
		93	Not done		

	WgtGrp (<i>hidden</i>) (<i>NR</i>)	(<i>A1</i>)
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Eligibility Criteria (Elig) *(form title/tab name)***Eligibility Criteria** *(section title)*

1.	Date of informed consent <i>(R, SV)</i>	/ / (2008-2020,DMY)
2.	Was the subject randomized in the study? <i>(R, SV)</i>	1 Passed, randomization criteria met / / : (2008-2020,DMYHM) 2 Failed, provide entry criteria not met: 5 Inclusion/Exclusion record # (A4 / A4 / A4 / A4 / A4 / A4 / A4) 8 Investigator decision 7 Subject decision
3.	Is your site participating in the Platelet Function Measurement Sub-study? <i>(R)</i>	1 Yes. Please enter the code that was sent to you (A8) 0 No
4.	Do you see a Visit tab labeled 'Neoplasm' on the Visit bar above [The Visit bar has the tabs labeled Vis1, Vis2, Vis3, Vis4, etc.].	1 Yes 0 No

Amendment B <i>(hidden)</i>	[mapped from IVR, read only - Amendment A = 1; Amendment B = 2]
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	Country <i>(hidden)</i> (NR)	(A2)
	Site <i>(hidden)</i> (NR)	(A4)
	Patient ID <i>(hidden)</i> (NR)	(A5)

	Patient Status <i>(hidden)</i> (NR)	(A20)
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UA/NSTEMI Index Event (Index) *(form title/tab name)***UA/NSTEMI Index Event: Location** *(section title)*

1.	Where did the subject present for evaluation of the index event? <i>(R)</i>	5 Hospital Emergency Room 6 Already Hospitalized for another reason 99 Other
2.	When did the subject present for evaluation of the index event? <i>(R, SV)</i>	/ / : (2008-2020,DMYHM)
3.	When was the subject discharged from this index hospitalization? <i>(R)</i>	/ / (2008-2020,DMY)

UA/NSTEMI Index Event: Symptoms *(section title)*

4.	Did the subject have chest discomfort or equivalent ischemic symptoms at rest for ≥ 10 minutes within 24 hours prior to presentation for evaluation of the index event? <i>(R)</i>	0 No 1 Yes
5.	When did the last episode of symptoms start before presentation for evaluation of the index event? <i>(R)</i>	/ / : (2008-2020,DMYHM)

UA/NSTEMI Index Event: Killip Class *(section title)*

6.	Identify the subject's Killip class at the time of presentation for evaluation of the index event. <i>(R)</i>	1 Killip I - No pulmonary congestion or shock 2 Killip II - Mild pulmonary congestion or S3 gallop 3 Killip III - Pulmonary edema 4 Killip IV - Hypotension and shock
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UA/NSTEMI Index Event: Procedures *(section title)*

7.	Which of the findings were present on any ECG within 24 hours after presentation for evaluation of the index event? <i>(R)</i>	<p>1 Check all that apply:</p> <p>62 New ST depression >1mm in at least 2 or more ECG leads</p> <p>57 New transient ST segment elevation</p> <p>58 New Left Bundle Branch Block (LBBB)</p> <p>59 New Right Bundle Branch Block (RBBB)</p> <p>60 New T wave inversion</p> <p>61 Paced Rhythm</p> <p>95 None of the above</p>
8.	Was coronary angiography performed for evaluation of the index event? <i>(R)</i>	<p>93 No, check reason:</p> <p>24 No angiographic facilities available</p> <p>2 Subject refused angiography</p> <p>25 Contraindication for angiography</p> <p>26 Known coronary anatomy not suitable for revascularization</p> <p>99 Other</p> <p>1 Yes, provide date and time of the coronary angiography</p> <p>/ /</p> <p>: (2008-2020,DMYUU)</p>
9.	If coronary angiography was performed, was a stenosis >50% found in at least 1 major coronary artery? <i>(NR)</i>	<p>93 No</p> <p>1 Yes, provide reason revascularization not performed</p> <p>26 Coronary anatomy not suitable for revascularization</p> <p>2 Subject declined revascularization</p> <p>22 Subject's co-morbidities precluded revascularization</p> <p>99 Other</p>
10.	Was the LVEF assessed by echocardiographic imaging? <i>(R)</i>	<p>96 No</p> <p>1 Yes</p> <p>% <i>(N9)</i></p> <p>97 Unknown</p>
11.	Was the LVEF assessed by nuclear imaging? <i>(R)</i>	<p>96 No</p> <p>1 Yes</p> <p>% <i>(N9)</i></p> <p>97 Unknown</p>

UA/NSTEMI Index Event: Lab Data *(section title)*

12.	What was the initial creatinine result (local lab)? <i>(R)</i>	<div>90 value <i>(N9.0)</i></div> <div>72 mg/dl</div> <div>411 umol/L</div> <div>71 mg/L</div> <div>391 mmol/L</div> <div>99 Other If 'Other' then specify</div> <div>(A50)</div> <div>93 Not done</div>
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Index Event Aspirin Therapy *(section title)*

13.	Has the subject taken aspirin therapy during 7 days prior to the presentation of the evaluation of the index event through discharge of the index hospitalization? <i>(R)</i>	<div>1 Yes</div> <div>93 No</div>
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Index Event Aspirin Therapy Reporting *(section title)*

	Sequence number	Total Daily Dose	Start Date	Stop Date
14.				

Index Event Aspirin Therapy Reporting Entry *(section title)*

14a	Sequence number <i>(NR, CALCULATED)</i>	
14b	Total daily dose <i>(R)</i>	mg <i>(N9)</i>
14c	Start date <i>(R)</i>	/ / <i>(1900-2020,UUY)</i>
14d	Stop date <i>(R)</i>	/ / <i>(2008-2020,DMY)</i>

Anticoagulant Medication for Use for Index Event *(section title)*

15.	Did the subject receive any anticoagulant medications for the treatment of the index event? <i>(R)</i>	<div>1 Yes</div> <div>93 No</div>
-----	--	-----------------------------------

Anticoagulant Medication Use for Index Event Reporting *(section title)*

	Name of anticoagulant medication	Start date	Stop date
16.			

Anticoagulant Medication Use for Index Event Reporting Entry *(section title)*

16a.	Name of anticoagulant medication <i>(R)</i>		
16b.	Start date <i>(R)</i>	/	/ <i>(1900-2020,DMY)</i>
16c.	Stop date <i>(R)</i>	/	/ <i>(2008-2020,DMY)</i>

GP IIb/IIIa Inhibitor Use for Index Event *(section title)*

17.	Did the subject receive any GP IIb/IIIa Inhibitors for the treatment of the index event? <i>(R)</i>	1	Yes
		93	No

GP IIb/IIIa Inhibitor Use for Index Event Reporting *(section title)*

	Name of GP IIb/IIIa inhibitor	Start date	Stop date
18.			

GP IIb/IIIa Inhibitor Use for Index Event Reporting Entry *(section title)*

18a.	Name of GP IIb/IIIa inhibitor <i>(R)</i>		
18b.	Start date <i>(R)</i>	/	/ <i>(1900-2020,DMY)</i>
18c.	Stop date <i>(R)</i>	/	/ <i>(2008-2020,DMY)</i>

Cardiac Biomarkers (CK,CK-MB,TROPONIN) *(section title)*

19.	Initial CK (R)	<p>1 Result (N9.0)</p> <p> Upper Limit of Normal (N9.0)</p> <p> If 'Other' then specify (A50)</p> <p> / /</p> <p> : (2008-2020,DMYHM)</p> <p>93 Not done</p>
20.	Peak CK (R)	<p>96 Same as initial result</p> <p>2 Result (N9.0)</p> <p> Upper Limit of Normal (N9.0)</p> <p> If 'Other' then specify (A50)</p> <p> / /</p> <p> : (2008-2020,DMYHM)</p> <p>93 Not done</p>
21.	Initial CK-MB (R)	<p>1 Result (N9.0)</p> <p> Upper Limit of Normal (N9.0)</p> <p> If 'Other' then specify (A50)</p> <p> / /</p> <p> : (2008-2020,DMYHM)</p> <p>93 Not done</p>
22.	Peak CK-MB (R)	<p>96 Same as initial result</p> <p>2 Result (N9.0)</p> <p> Upper Limit of Normal (N9.0)</p> <p> If 'Other' then specify (A50)</p> <p> / /</p> <p> : (2008-2020,DMYHM)</p> <p>93 Not done</p>
23.	Initial Troponin I (R)	<p>1 Result (N9.0)</p> <p> Upper Limit of Normal (N9.0)</p> <p> If 'Other' then specify (A50)</p> <p> / /</p> <p> : (2008-2020,DMYHM)</p> <p>93 Not done</p>

24.	Peak Troponin I (R)	<div>96 Same as initial result</div> <div>2 Result (N9.0)</div> <div>Upper Limit of Normal (N9.0)</div> <div>If 'Other' then specify (A50)</div> <div>/ /</div> <div>: (2008-2020,DMYHM)</div> <div>93 Not done</div>
25.	Initial Troponin T (R)	<div>1 Result (N9.0)</div> <div>Upper Limit of Normal (N9.0)</div> <div>If 'Other' then specify (A50)</div> <div>/ /</div> <div>: (2008-2020,DMYHM)</div> <div>93 Not done</div>
26.	Peak Troponin T (R)	<div>96 Same as initial result</div> <div>2 Result (N9.0)</div> <div>Upper Limit of Normal (N9.0)</div> <div>If 'Other' then specify (A50)</div> <div>/ /</div> <div>: (2008-2020,DMYHM)</div> <div>93 Not done</div>

Pulldown List 1

Value	Label
1	Unfractionated Heparin
2	Low Molecular Weight Heparin
3	Bivalirudin
4	Hirudin
5	Fondaparinux
6	Argatroban
99	Other

Pulldown List 2

Value	Label
1	Abciximab

2	Eptifibatide
3	Tirofiban

Pulldown List 3	
Value	Label
111	ug/L
153	ng/mL
231	U/L
311	IU/L
253	mU/mL
331	mIU/mL
202	uKat/L
99	Other

UA/NSTEMI Index Event (Index) *(form title/tab name)***UA/NSTEMI Index Event: Location** *(section title)*

1.	Where did the subject present for evaluation of the index event? <i>(R)</i>	5 Hospital Emergency Room 6 Already Hospitalized for another reason 99 Other
2.	When did the subject present for evaluation of the index event? <i>(R, SV)</i>	/ / : (2008-2020,DMYHM)
3.	When was the subject discharged from this index hospitalization? <i>(R)</i>	/ / (2008-2020,DMY)

UA/NSTEMI Index Event: Symptoms *(section title)*

4.	Did the subject have chest discomfort or anginal equivalent symptoms at rest for ≥ 5 minutes within 24 hours prior to presentation for evaluation of the index event? <i>(R)</i>	0 No 1 Yes
5.	When did the last episode of symptoms start before presentation for evaluation of the index event? <i>(R)</i>	/ / : (2008-2020,DMYHM)

UA/NSTEMI Index Event: Killip Class *(section title)*

6.	Identify the subject's Killip class at the time of presentation for evaluation of the index event. <i>(R)</i>	1 Killip I - No pulmonary congestion or shock 2 Killip II - Mild pulmonary congestion or S3 gallop 3 Killip III - Pulmonary edema 4 Killip IV - Hypotension and shock
----	---	--

UA/NSTEMI Index Event: Procedures *(section title)*

7.	Which of the findings were present on any ECG within 24 hours after presentation for evaluation of the index event? (R)	<p>1 Check all that apply:</p> <p>62 New ST depression >1mm in at least 2 or more ECG leads</p> <p>57 New transient ST segment elevation</p> <p>58 New Left Bundle Branch Block (LBBB)</p> <p>59 New Right Bundle Branch Block (RBBB)</p> <p>60 New T wave inversion</p> <p>61 Paced Rhythm</p> <p>95 None of the above</p>
8.	Was coronary angiography performed for evaluation of the index event? (R)	<p>93 No, check reason:</p> <p>24 No angiographic facilities available</p> <p>2 Subject refused angiography</p> <p>25 Contraindication for angiography</p> <p>26 Known coronary anatomy not suitable for revascularization</p> <p>99 Other</p> <p>1 Yes, provide date and time of the coronary angiography</p> <p>/ /</p> <p>: (2008-2020,DMYUU)</p>
9.	If coronary angiography was performed, was a stenosis greater than or equal to 30% found in any native coronary vessel? (NR)	<p>93 No</p> <p>1 Yes, provide reason revascularization not performed</p> <p>26 Coronary anatomy not suitable for revascularization</p> <p>2 Subject declined revascularization</p> <p>22 Subject's co-morbidities precluded revascularization</p> <p>99 Other</p>
10.	Was the LVEF assessed by echocardiographic imaging? (R)	<p>96 No</p> <p>1 Yes</p> <p>% (N9)</p> <p>97 Unknown</p>
11.	Was the LVEF assessed by nuclear imaging? (R)	<p>96 No</p> <p>1 Yes</p> <p>% (N9)</p> <p>97 Unknown</p>

UA/NSTEMI Index Event: Lab Data (section title)

12.	What was the initial creatinine result (local lab)? <i>(R)</i>	<div>90 value <i>(N9.0)</i></div> <div>72 mg/dl</div> <div>411 umol/L</div> <div>71 mg/L</div> <div>391 mmol/L</div> <div>99 Other If 'Other' then specify</div> <div>(A50)</div> <div>93 Not done</div>
-----	--	--

Index Event Aspirin Therapy *(section title)*

13.	Has the subject taken aspirin therapy during 7 days prior to the presentation of the evaluation of the index event through discharge of the index hospitalization? <i>(R)</i>	<div>1 Yes</div> <div>93 No</div>
-----	---	-----------------------------------

Index Event Aspirin Therapy Reporting *(section title)*

	Sequence number	Total Daily Dose	Start Date	Stop Date
14.				

Index Event Aspirin Therapy Reporting Entry *(section title)*

14a	Sequence number <i>(NR, CALCULATED)</i>	
14b	Total daily dose <i>(R)</i>	mg <i>(N9)</i>
14c	Start date <i>(R)</i>	/ / <i>(1900-2020,UUY)</i>
14d	Stop date <i>(R)</i>	/ / <i>(2008-2020,DMY)</i>

Anticoagulant Medication for Use for Index Event *(section title)*

15.	Did the subject receive any anticoagulant medications for the treatment of the index event? <i>(R)</i>	<div>1 Yes</div> <div>93 No</div>
-----	--	-----------------------------------

Anticoagulant Medication Use for Index Event Reporting *(section title)*

	Name of anticoagulant medication	Start date	Stop date
16.			

Anticoagulant Medication Use for Index Event Reporting Entry *(section title)*

16a.	Name of anticoagulant medication <i>(R)</i>	
16b.	Start date <i>(R)</i>	/ / <i>(1900-2020,DMY)</i>
16c.	Stop date <i>(R)</i>	/ / <i>(2008-2020,DMY)</i>

GP IIb/IIIa Inhibitor Use for Index Event *(section title)*

17.	Did the subject receive any GP IIb/IIIa Inhibitors for the treatment of the index event? <i>(R)</i>	1 Yes 93 No
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GP IIb/IIIa Inhibitor Use for Index Event Reporting *(section title)*

	Name of GP IIb/IIIa inhibitor	Start date	Stop date
18.			

GP IIb/IIIa Inhibitor Use for Index Event Reporting Entry *(section title)*

18a.	Name of GP IIb/IIIa inhibitor <i>(R)</i>	
18b.	Start date <i>(R)</i>	/ / <i>(1900-2020,DMY)</i>
18c.	Stop date <i>(R)</i>	/ / <i>(2008-2020,DMY)</i>

Cardiac Biomarkers (CK,CK-MB,TROPONIN) *(section title)*

19.	Initial CK (R)	<p>1 Result (N9.0)</p> <p> Upper Limit of Normal (N9.0)</p> <p> If 'Other' then specify (A50)</p> <p> / /</p> <p> : (2008-2020,DMYHM)</p> <p>93 Not done</p>
20.	Peak CK (R)	<p>96 Same as initial result</p> <p>2 Result (N9.0)</p> <p> Upper Limit of Normal (N9.0)</p> <p> If 'Other' then specify (A50)</p> <p> / /</p> <p> : (2008-2020,DMYHM)</p> <p>93 Not done</p>
21.	Initial CK-MB (R)	<p>1 Result (N9.0)</p> <p> Upper Limit of Normal (N9.0)</p> <p> If 'Other' then specify (A50)</p> <p> / /</p> <p> : (2008-2020,DMYHM)</p> <p>93 Not done</p>
22.	Peak CK-MB (R)	<p>96 Same as initial result</p> <p>2 Result (N9.0)</p> <p> Upper Limit of Normal (N9.0)</p> <p> If 'Other' then specify (A50)</p> <p> / /</p> <p> : (2008-2020,DMYHM)</p> <p>93 Not done</p>
23.	Initial Troponin I (R)	<p>1 Result (N9.0)</p> <p> Upper Limit of Normal (N9.0)</p> <p> If 'Other' then specify (A50)</p> <p> / /</p> <p> : (2008-2020,DMYHM)</p> <p>93 Not done</p>

24.	Peak Troponin I (R)	<div>96 Same as initial result</div> <div>2 Result (N9.0)</div> <div>Upper Limit of Normal (N9.0)</div> <div>If 'Other' then specify (A50)</div> <div>/ /</div> <div>: (2008-2020,DMYHM)</div> <div>93 Not done</div>
25.	Initial Troponin T (R)	<div>1 Result (N9.0)</div> <div>Upper Limit of Normal (N9.0)</div> <div>If 'Other' then specify (A50)</div> <div>/ /</div> <div>: (2008-2020,DMYHM)</div> <div>93 Not done</div>
26.	Peak Troponin T (R)	<div>96 Same as initial result</div> <div>2 Result (N9.0)</div> <div>Upper Limit of Normal (N9.0)</div> <div>If 'Other' then specify (A50)</div> <div>/ /</div> <div>: (2008-2020,DMYHM)</div> <div>93 Not done</div>

Pulldown List 1

Value	Label
1	Unfractionated Heparin
2	Low Molecular Weight Heparin
3	Bivalirudin
4	Hirudin
5	Fondaparinux
6	Argatroban
99	Other

Pulldown List 2

Value	Label
1	Abciximab

2	Eptifibatide
3	Tirofiban

Pulldown List 3	
Value	Label
111	ug/L
153	ng/mL
231	U/L
311	IU/L
253	mU/mL
331	mIU/mL
202	uKat/L
99	Other

Commercial Clopidogrel Use at Index (Clopid) *(form title/tab name)***Commercial Clopidogrel Use at Index** *(section title)*

1.	Did subject receive a maintenance dose of commercial clopidogrel for at least 5 continuous days prior to presentation? <i>(R,SV)</i>	0 No 1 Yes, provide dose: 100 75 mg 101 150 mg 102 greater than 150 mg
2.	Did subject receive a loading dose of commercial clopidogrel within five days prior to presentation? <i>(R,SV)</i>	0 No 1 Yes, provide date and time: / / : <i>(2008-2020,DMYUU)</i> 103 less than 300 mg 104 300 mg 105 600 mg 106 greater than 600 mg
3.	Did subject receive a dose of commercial clopidogrel in the first 24 hours following presentation? <i>(R,SV)</i>	0 No 1 Yes, provide date and time: / / : <i>(2008-2020,DMYHM)</i> 100 75 mg 101 150 mg 104 300 mg 105 600 mg 106 greater than 600 mg

4.	Beyond 24 hours of presentation, did subject-receive commercial clopidogrel daily until randomization? (R)	0	No
		1	Yes, provide dose:
		100	75 mg
		101	150 mg
		102	greater than 150 mg

Commercial Clopidogrel Use at Index (Clopid) *(form title/tab name)*

Commercial Clopidogrel Use at Index *(section title)*

1.	Did subject receive a maintenance dose of commercial clopidogrel for at least 5 continuous days prior to presentation? <i>(R,SV)</i>	<div>0 No</div> <div>1 Yes, provide dose:</div> <div>100 75 mg</div> <div>101 150 mg</div> <div>102 greater than 150 mg</div>
2.	Did subject receive a loading dose of commercial clopidogrel within five days prior to presentation? <i>(R,SV)</i>	<div>0 No</div> <div>1 Yes, provide date and time:</div> <div>/ /</div> <div>: <i>(2008-2020,DMYUU)</i></div> <div>103 less than 300 mg</div> <div>104 300 mg</div> <div>105 600 mg</div> <div>106 greater than 600 mg</div>
3.	Did subject receive a dose of commercial clopidogrel in the first 72 hours following presentation? <i>(R,SV)</i>	<div>0 No</div> <div>1 Yes, provide date and time:</div> <div>/ /</div> <div>: <i>(2008-2020,DMYHM)</i></div> <div>100 75 mg</div> <div>101 150 mg</div> <div>104 300 mg</div> <div>105 600 mg</div> <div>106 greater than 600 mg</div>

4.	Beyond 72 hours of presentation, did subject-receive commercial clopidogrel daily until randomization? (R)	0	No
		1	Yes, provide dose:
		100	75 mg
		101	150 mg
		102	greater than 150 mg

Medical History (MedHs) *(form title / tab name)*
Medical History *(section title)*

1.	Family history of Coronary Artery Disease (CAD) (R)	1 Yes 0 No 97 Unknown
2.	Diabetes Mellitus (R)	0 No 1 Yes, treated with: 3 Insulin 2 Oral agents 1 Dietary control 95 Yes, not treated 97 Unknown
3.	Hypertension (R)	1 Yes 0 No 97 Unknown
4.	Hyperlipidemia (R)	1 Yes 0 No 97 Unknown
5.	Peripheral Artery Disease (PAD) (R)	1 Yes 0 No 97 Unknown
6.	Prior TIA (R)	1 Yes 0 No 97 Unknown
7.	Prior Ischemic Stroke (R)	1 Yes 0 No 97 Unknown

8.	Other manifestation of cerebrovascular disease (R)	1 Yes 0 No 97 Unknown
9.	Prior myocardial infarction (R)	1 Yes 0 No 97 Unknown
10.	Documentation of a coronary stenosis >50% prior to presentation for evaluation of the index event (R)	1 Yes 0 No 97 Unknown
11.	Chronic heart failure (R)	1 Yes 0 No 97 Unknown
12.	Has the subject ever had atrial fibrillation? (R)	1 Yes 5 Past 1 Current 0 No 97 Unknown
13.	Chronic renal insufficiency (R)	1 Yes 0 No 97 Unknown
14.	History of peptic ulcer disease (R)	1 Yes 0 No 97 Unknown

Medical History Procedures (section title)

15.	Did the subject have a lower extremity amputation to treat PAD? (R)	1 Yes 0 No 97 Unknown
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16.	Did the subject have prior revascularization of an iliac or femoral artery? <i>(R)</i>	1 Yes 0 No 97 Unknown
17.	Has a carotid artery revascularization procedure been performed? <i>(R)</i>	1 Yes 0 No 97 Unknown
18.	Prior Percutaneous Coronary Intervention (PCI) <i>(R)</i>	1 Yes, provide month and year of most recent Percutaneous Coronary Intervention / <i>(1900-2020,UY)</i> 0 No 97 Unknown
19.	Has a coronary stent ever been implanted prior to randomization in the study? <i>(R)</i>	1 Yes 0 No 97 Unknown
20.	Prior CABG <i>(R)</i>	1 Yes, provide month and year of most recent CABG / <i>(1900-2020,UY)</i> 0 No 97 Unknown

Stent information *(section title)*

	Date of Stent Implantation	Vessel Type	Location of Stent	Diameter of vessel stented	Type of stent	Stent length	Stent diameter	Was this stent overlapped with another stent?
21a.								

Stent information Entry *(section title)*

Date of Stent implantation (R)	90 / / (1900-2020,UUY) 97 Unknown
Vessel type (R, SV)	490 Native coronary artery 489 Saphenous vein bypass graft 13 Arterial bypass graft 97 Unknown
Location of stent (R, SV)	
Diameter of vessel stented (R)	90 mm (N11.1) 97 Unknown
Type of stent (R, SV)	79 Drug eluting stent (DES) 77 Bare Metal stent (BMS) 99 Other 97 Unknown
Stent length (R)	90 mm (N11.1) 97 Unknown
Stent diameter (R)	90 mm (N11.1) 97 Unknown
Was this stent overlapped with another stent? (R)	1 Yes 0 No 97 Unknown 96 Not applicable

Tobacco Use (section title)

22.	Has the subject ever used tobacco products? (R)	0 No 1 Yes, how many years? # of years (N2) 98 Not assessed
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23.	If the subject used tobacco products before, has the subject used tobacco products within 30 days prior to randomization? (NR)	0 No, specify stop date / (1900-2020,UY) 1 Yes 9 Cigarettes # per day (N3) 5 Cigars 8 Pipes 26 Nicotine patch/gum 11 Smokeless/chewing tobacco
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Frailty Characteristics (section title)

24.	If the subject is 65 years of age or older at the time of randomization, check all that apply. (R)	90 Within the last 12 months has the subject experienced any of the following: 1 Unintentional weight loss (greater than or equal to 5kg/10 lbs) 2 Developed decreased grip strength 3 Developed increasing fatigue/lethargy or declining endurance 4 Walks a distance of 5 m/15 feet at a slower pace 5 Decline in typical physical activity level 96 Not applicable (subject is less than 65 years old OR none of the above)
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Pulldown List 1	
Value	Label
1	1, Proximal right coronary artery conduit segment
2	2, Mid-right coronary artery conduit segment
3	3, Distal right coronary artery conduit segment
4	4, Right posterior descending artery segment
5	5, Right posterior atrioventricular segment
6	6, First right posterolateral segment
7	7, Second right posterolateral segment
8	8, Third right posterolateral segment
9	9, Posterior descending septal perforators segment

10	10, Acute marginal segment (s)
11	11, Left main coronary artery segment
12	12, Proximal LAD artery segment
13	13, Mid-LAD artery segment
14	14, Distal LAD artery segment
15	15, First diagonal branch segment
16	15a, Lateral first diagonal branch segment
17	16, Second diagonal branch segment
18	16a, Lateral second diagonal branch segment
19	17, LAD septal perforators segment
20	18, Proximal circumflex artery segment
21	19, Mid-circumflex artery segment
22	19a, Distal circumflex artery segment
23	20, First obtuse marginal branch segment
24	20a, Lateral first obtuse marginal branch segment
25	21, Second obtuse marginal branch segment
26	21a, Lateral second obtuse marginal branch segment
27	22, Third obtuse marginal branch segment
28	22a, Lateral third obtuse marginal branch segment
29	23, Circumflex artery AV groove continuation segment
30	24, First left posterolateral branch segment
31	25, Second left posterolateral branch segment
32	26, Third posterolateral descending artery segment
33	27, Left posterolateral descending artery segment
34	28, Ramus intermedius segment
35	28a, Lateral ramus intermedius segment
36	29, Third diagonal branch segment
37	29a, Lateral third diagonal branch segment
97	Unknown

Atrial Fibrillation (Atrial) (*form title / tab name*)**Atrial Fibrillation** (*section title*)

1.	Duration of the atrial fibrillation: (R)	months (N 9.1)
2.	Were there any previous thromboembolic events associated with atrial fibrillation before randomization? (R)	1 Yes 0 No 97 Unknown
3.	Was the subject previously treated with oral anticoagulants before randomization? (R)	1 Yes 0 No 97 Unknown
4.	Was the oral anticoagulant stopped due to a bleeding complication? (NR)	1 Yes 0 No 97 Unknown
5.	Was the subject treated with an antiarrhythmic agent within the previous 12 months before randomization? (R)	1 Yes 0 No 97 Unknown

Procedures (*section title*)

6.	Were there any previous cardioversion attempts within the last 12 months before randomization? (R)	1 Yes 0 No 97 Unknown
7.	Did the subject undergo ablation for the atrial fibrillation before randomization? (R)	1 Yes 0 No 97 Unknown

Renal Insufficiency (Renal) *(form title / tab name)***Renal Insufficiency** *(section title)*

1.	Does the subject have a documented history of contrast induced nephropathy? <i>(R)</i>	1 Yes 0 No 97 Unknown
2.	Did the subject have documented proteinuria during the index event/hospitalization? <i>(R)</i>	1 Yes 0 No
3.	Did the subject have anemia associated with the chronic renal insufficiency within 30 days prior to the index hospitalization? <i>(R)</i>	1 Yes 0 No 97 Unknown
4.	Did the subject receive a dose of erythropoietin to treat the anemia associated with the chronic renal insufficiency? <i>(NR)</i>	1 Yes 0 No 97 Unknown

Vital Signs (Vital) *(form title/tab name)***Vital Signs** *(section title)*

1.	Blood pressure (R)	90	/	mmHg (N3) /(N3)
			Systolic Diastolic	
		93	Not done	
2.	Heart rate (R)	90	bpm (N3)	
		93	Not done	

12-Lead ECG (Ecg) *(form title/tab name)***12-Lead ECG** *(section title)*

1.	Date and time ECG performed (R)	<div data-bbox="654 573 686 604">90</div> <div data-bbox="841 573 857 604">/</div> <div data-bbox="938 573 954 604">/</div> <div data-bbox="885 636 901 667">:</div> <div data-bbox="1003 636 1271 667">(2008-2020,DMYHM)</div> <div data-bbox="654 688 686 720">93</div> <div data-bbox="748 688 898 720">Not done</div>
2.	Since the previous study ECG, were there any new abnormalities? <i>(NR)</i>	<div data-bbox="654 768 670 800">1</div> <div data-bbox="716 758 1117 800">Yes, check all that apply</div> <div data-bbox="708 814 740 846">66</div> <div data-bbox="792 814 1230 856">New ST depression >1mm</div> <div data-bbox="708 873 740 905">57</div> <div data-bbox="792 873 1235 915">New ST segment elevation</div> <div data-bbox="708 930 740 961">58</div> <div data-bbox="792 930 1422 972">New Left Bundle Branch Block (LBBB)</div> <div data-bbox="708 989 740 1020">59</div> <div data-bbox="792 989 1463 1031">New Right Bundle Branch Block (RBBB)</div> <div data-bbox="708 1045 740 1077">60</div> <div data-bbox="792 1045 1154 1087">New T wave inversion</div> <div data-bbox="708 1104 740 1136">65</div> <div data-bbox="792 1104 1003 1146">New Q wave</div> <div data-bbox="708 1161 740 1192">61</div> <div data-bbox="792 1161 1019 1203">Paced rhythm</div> <div data-bbox="708 1220 740 1251">99</div> <div data-bbox="792 1220 886 1262">Other</div> <div data-bbox="654 1266 670 1297">0</div> <div data-bbox="716 1266 768 1297">No</div>

Verify Now Platelet Function Measurements (PFM) *(form title/tab name)***Verify Now Platelet Function Measurements** *(section title)****Please note: The results from the Verify Now device are encrypted.***

1.	Pre-study drug dose P2Y ₁₂ assay: (R, SV)	<div>90</div> <div>/ /</div> <div>:</div> <div>(2008-2020,DMYHM)</div> <div>Result (encrypted):</div> <div>PRU (A20)</div> <div>% Inhibition (A20)</div> <div>Base (A20)</div> <div>93</div> <div>Not done</div> <div>Error/attention message received</div>
2.	Post-study drug dose P2Y ₁₂ assay: (R, SV)	<div>90</div> <div>/ /</div> <div>:</div> <div>(2008-2020,DMYHM)</div> <div>Result (encrypted):</div> <div>PRU (A20)</div> <div>% Inhibition (A20)</div> <div>Base (A20)</div> <div>93</div> <div>Not done</div> <div>Error/attention message received</div>

3.	ASA (aspirin) assay: (R)	90 / / : (2008-2020,DMYHM) Result (encrypted): ARU (A20) 93 Not done Error/attention message received
4.	Date and time of pre-dose specimen collection: (R, SV)	90 / / : (2008-2020,DMYHM) 93 Not done
5.	Date and time of post-dose specimen collection: (R, SV)	90 / / : (2008-2020,DMYHM) 93 Not done

Verify Now Platelet Function Measurements (PFM2) *(form title/tab name)***Verify Now Platelet Function Measurements** *(section title)****Please note: The results from the Verify Now device are encrypted.***

	Visit number (R) [Mapped from VISIT REFNAME]	— Programming note: Changed To A Control Box (A20)
1.	P2Y ₁₂ assay: (R, SV)	90 / / : (2008-2020,DMYHM) Result (encrypted): PRU (A20) % Inhibition (A20) Base (A20) 93 Not done Error/attention message received
2.	ASA (aspirin) assay: (R)	90 / / : (2008-2020,DMYHM) Result (encrypted): ARU (A20) 93 Not done Error/attention message received
3.	Date and time of specimen collection: (R, SV)	90 / / : (2008-2020,DMYHM) 93 Not done

Last study drug maintenance dose reporting *(section title)*

4.	Date and time of most recent study drug maintenance dose? <i>(R,SV)</i>	/ / : <i>(2008-2020,DMYHM)</i>
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Tobacco Habit (Tobacco) *(form title/tab name)***Tobacco Habit** *(section title)*

1.	Is the subject a current tobacco user? (R)	0 No
		1 Yes
		9 Cigarettes
		# per day (N3)
		5 Cigars
		8 Pipes
		26 Nicotine patch/gum
		11 Smokeless/chewing tobacco
		98 Not assessed

Study Drug Accountability (Dose) *(form title/tab name)***Study Drug Accountability** *(section title)*

1.	Did the subject receive study drug? <i>(R, SV)</i>	1 Yes, provide date and time of first study drug dose / / : <i>(2008-2020,DMYHM)</i> 93 No
2.	Type of first dose of study drug received by subject <i>(R, SV)</i>	18 Loading dose 19 Maintenance dose

Study Drug Accountability Reporting *(section title)*

	Visit #	Date study drug tablets dispensed	Type of first dose of study drug received by subject	Did subject receive the correct study drug kit?	Number of beige or yellow, double arrow shaped tablets returned	Number of pink, round shaped tablets returned
3.a			<i>(CALCULATED)</i>			
3.b			<i>(CALCULATED)</i>			
3.c			<i>(CALCULATED)</i>			

Study Drug Accountability Reporting Entry *(section title)*

Visit number <i>(MAPPED FROM VISIT REFNAME)</i>	<i>Programming Note: Changed To A Control Box- (A20)</i>
Date study drug tablets dispensed? <i>(R)</i>	1 / / <i>(2008-2020,DMY)</i> 96 Not applicable
Type of first dose of study drug received by subject <i>[read only]</i>	
Did subject receive the correct study drug kit? <i>(R, SV)</i>	96 Not applicable 1 Yes 0 No, comment below: (A200)

Number of beige or yellow, double arrow shaped tablets returned (record "0" if study drug kit is returned empty). <i>(R, SV)</i>	<div data-bbox="748 60 1593 268"><div>2 Tablets returned</div><div># of tablets returned <i>(N3)</i></div><div>3 Missing tablets</div><div># of tablets missing <i>(N3)</i></div></div>
Number of pink, round shaped tablets returned (record "0" if study drug kit is returned empty). <i>(R, SV)</i>	<div data-bbox="748 268 1593 476"><div>2 Tablets returned</div><div># of tablets returned <i>(N3)</i></div><div>3 Missing tablets</div><div># of tablets missing <i>(N3)</i></div></div>

Study Drug Interruptions/Discontinuation (Interrupt) *(form title/tab name)***Study Drug Interruptions/Discontinuation** *(section title)*

1.	Has the study drug been interrupted OR has the study drug been permanently discontinued? <i>(R)</i>	1 Yes	93 No
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Study Drug Interruptions/Discontinuation *(section title)*

	First Date that Study Drug Was Not Taken	Primary Reason for Interruption	Primary Reason for Discontinuation	Date Study Drug Restarted	Will subject remain in the study?
2.a					

Study Drug Interruptions/Discontinuation Entry *(section title)*

First date that study drug was not taken <i>(R, SV)</i>	/ / (2008-2020,DMY)

Primary reason for interruption (R, SV)	<p>17 Subject had a procedure</p> <p>E (N5)</p> <p>1 Adverse event</p> <p>E (N5)</p> <p>18 Drug temporarily lost or misplaced</p> <p>20 Need for oral anticoagulation</p> <p>14 Investigator decision not related to AE</p> <p>6 Subject decision not related to AE</p> <p>96 Not applicable</p>
Primary reason for discontinuation (R, SV)	<p>19 Subject had a procedure</p> <p>E (N5)</p> <p>4 Adverse event</p> <p>E (N5)</p> <p>14 Need for oral anticoagulation</p> <p>18 Investigator decision not related to AE</p> <p>9 Subject decision not related to AE</p> <p>31 Study drug unblinded by the investigator (not related to AE)</p> <p>21 Entry criteria not met</p> <p>22 Lost to follow up</p> <p>96 Not applicable</p>
Date study drug restarted (R, SV)	<p>90 / / (2008-2020,DMY)</p> <p>96 Study drug discontinued permanently</p>
If study drug was discontinued permanently, will the subject remain in the study to be followed for endpoints and adverse events? (NR)	<p>1 Yes</p> <p>0 No</p>

Transfusion (Trans) (form title/tab name)

Transfusions (section title)

1.	Did the subject receive transfusions during the study? (R)	1 Yes	0 No
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Transfusions (section title)

	Sequence Number	Type of Transfusion	Amount of Transfusion	Date and time of Transfusion
2.a				

Transfusions Entry (section title)

Sequence number [hidden, CALCULATED]			
Type of transfusion (R, SV)			
Amount of transfusion (R, SV)	(N9.0)	Units	cc (mL)
Date and time initial unit transfused (R, SV)	/ / : (2008-2020, DMYHM)		

Pulldown List 1	
Value	Label

1	Packed red blood cells
3	Whole blood
4	Platelets
6	Fresh frozen plasma
8	Cryoprecipitate
99	Other

EQ5D (EQ5D) *(form title/tab name)***EQ5D** *(section title)*

1.	Date of assessment (R)	90 / / (2008-2020,DMY)
		93 Not done

EQ5D Scale *(section title)*

2.	Mobility (NR)	1 I have no problems in walking about 2 I have some problems in walking about 3 I am confined to bed
3.	Self-care (NR)	1 I have no problems with self-care 2 I have some problems washing or dressing myself 3 I am unable to wash or dress myself
4.	Usual Activities (NR)	1 I have no problems with performing my usual activities 2 I have some problems performing my usual activities 3 I am unable to perform my usual activities
5.	Pain/Discomfort (NR)	1 I have no pain or discomfort 2 I have moderate pain or discomfort 3 I have extreme pain or discomfort
6.	Anxiety/Depression (NR)	1 I am not anxious or depressed 2 I am moderately anxious or depressed 3 I am extremely anxious or depressed
7.	Health State Score (NR)	(N3)

DNA Banking (DNA) *(form title/tab name)***DNA Banking** *(section title)*

1.	Date of DNA consent <i>(R)</i>	90 / / <i>(2008-2020,DMY)</i> 98 Not obtained for this subject
2.	Maternal grandfather <i>(NR)</i>	98 Information not obtained 1 Origin obtained
3.	Maternal grandmother <i>(NR)</i>	98 Information not obtained 1 Origin obtained
4.	Paternal grandfather <i>(NR)</i>	98 Information not obtained 1 Origin obtained
5.	Paternal grandmother <i>(NR)</i>	98 Information not obtained 1 Origin obtained

Pulldown List 1	
Value	Label
1001	Afghanistani
1002	African
1003	African American
1071	African, Central

1072	African, North
1073	African, South
1004	Aleutian Islander
1005	American Eskimo
1006	American Not otherwise specified
1007	Australian
1008	Australian Aboriginal
1009	Austrian
1010	Belgian
1011	Brazilian
1012	Canadian
1013	Caribbean or West Indian (Non Spanish speaking)
1014	Caribbean or West Indian (Spanish speaking)
1015	Chinese
1074	Achang
1075	Bai
1076	Blang
1077	Bonan
1078	Buyei
1079	Chosen
1080	Dai
1081	Daur
1082	De'ang
1083	Derung
1084	Dong
1085	Dongxiang
1086	Ewenki
1087	Gaoshan
1088	Gelao

1089	Gin
1070	Han
1090	Hani
1091	Hezhan
1092	Hui
1093	Jingpo
1094	Jino
1095	Kazak
1096	Kirgiz
1097	Lahu
1098	Lhoba
1099	Li
1100	Lisu
1101	Manchu
1102	Maonan
1103	Miao
1104	Monba
1105	Mongol
1106	Mulao
1107	Naxi
1108	Nu
1109	Oroqen
1110	Pumi
1111	Qiang
1112	Russ
1113	Salar
1114	She
1115	Sui
1116	Tajik
1117	Tatar
1118	Tibetan
1119	Tu

1120	Tujia
1121	Uygur
1122	Uzbek
1123	Va
1124	Xibe
1125	Yao
1126	Yi
1127	Yugur
1128	Zhuang
1016	Cuban
1017	Czech
1018	Danish
1019	Dutch
1020	English
1021	Filipino
1022	Finnish
1023	French
1024	German
1068	Greek
1025	Guamanian
1026	Hungarian
1027	Indian
1028	Indonesian
1029	Iranian
1030	Iraqi
1031	Irish
1032	Israeli
1033	Italian
1034	Japanese
1129	Ainu

1130	Ryukyuan
1035	Jordanian
1036	Korean
1037	Lebanese
1038	Malaysian
1039	Mexican
1040	Native American
1041	New Zealander
1042	Norwegian
1043	Pakistani
1044	Peruvian
1045	Polish
1046	Portuguese
1047	Puerto Rican
1048	Russian
1049	Samoan
1050	Scottish
1051	Spanish
1052	Slovakian
1053	Swedish
1054	Swiss
1055	Taiwanese
1056	Torres Strait Islander
1057	Turkish
1058	Vietnamese
1059	Welsh
1060	Yugoslavian
1069	Chinese, not Han
1061	Other Central American (eg. Nicaraguan, Guatemalan)

1062	Other South American (eg. Chilean, Colombian)
1063	Other Western European
1064	Other East European (eg. Romanian, Bulgarian, Albanian)
1065	Other Middle Eastern (eg. Arabian Saudi, Kuwaiti, Qatari, Syrian, Omani)
1066	Other Asian (eg. Thai, Laotian, Cambodian, Burmese)
1067	Other Pacific Islander (eg. Okinawan, Tahitian)
99	Other
97	Unknown

Cardiac Diagnostic Catheterization/Procedures (DiagCath) *(form title/tab name)*

(Repeating Form)

Date and time of diagnostic catheterization	Type of procedure(s) performed	Access site	Left Ventricular Ejection Fraction (LVEF) by contrast ventriculography	Date and time sheath pulled	Access site closure method	Native coronary vessel(s) with 50% diameter stenosis	Other vessel type(s) with >50% diameter stenosis	Was a stent thrombosis identified?	Did a hematoma occur at the access site?

Cardiac Diagnostic Catheterization/Procedures *(section title)*

1.	Date and time of diagnostic catheterization <i>(R)</i>	90 / / : (2008-2020,DMYUU) 97 Unknown
2.	Type of procedure(s) performed <i>(R)</i>	1 Check all that apply: 1 Left heart catheterization 2 Right heart catheterization 182 Coronary angiography 97 Unknown
3.	Access site <i>(R)</i>	1 Check all that apply: 19 Femoral artery 487 Femoral vein 21 Radial artery 14 Brachial artery 99 Other 97 Unknown

4.	Left Ventricular Ejection Fraction (LVEF) by contrast ventriculography (R)	90 % (N9) 97 Unknown 93 Not done
5.	Date and time sheath pulled (R)	90 / / : (2008-2020,DMYUU) 97 Unknown 96 Not pulled
6.	Access site closure method (R)	89 Mechanical pressure device 90 Closure device 88 Manual pressure 97 Unknown

Diagnosis (section title)

7.	Native coronary vessel(s) with greater than or equal to 50% diameter stenosis (R)	1 Check all that apply: 38 Left Anterior Descending Coronary Artery (LAD) 39 Right Coronary Artery (RCA) 40 Left Circumflex Coronary Artery (LCX) 11 Left Main Coronary Artery 97 Unknown 95 None
8.	Other vessel type(s) with greater than or equal to 50% diameter stenosis (R)	1 Check all that apply: 489 Saphenous vein bypass graft 13 Arterial bypass graft 99 Other 97 Unknown 95 None
9.	Was a stent thrombosis identified? (R)	0 No 1 Yes 97 Unknown
11.	Circumstance	2 Elective 6 Urgent/Emergent

10.	Did a hematoma occur at the access site? (R)	0	No
		1	Yes, provide date and time that hematoma was first noted: / / : (2008-2020,DMYUU)
		97	Unknown

Coronary Artery Bypass Graft Surgery (CABG) (*form title/tab name*)**Coronary Artery Bypass Graft Surgery (CABG)** (*section title*)

Circumstance:	<i>Hospital Tracking Number</i>	Date and time of CABG procedure	Which vessels were by-passed?	Did this procedure require a re-exploration for bleeding?	Were any cardiac biomarkers elevated greater than 5 times the upper limit of normal within 24 hours following the procedure?

Coronary Artery Bypass Graft Surgery (CABG) (*section title*)

1.	Circumstance: (<i>R</i>)	2	Elective
		6	Urgent/Emergent
2.	Hospital Tracking Number (<i>R</i>)	90	H (<i>N5</i>)
		96	Not applicable

Procedures (*section title*)

3.	Date and time of CABG procedure (<i>R, SV</i>)	/ /
		: (<i>2008-2020,DMYUU</i>)
4.	Which vessels were by-passed? (<i>R</i>)	1 Check all that apply: 38 Left Anterior Descending Coronary artery (LAD) 39 Right Coronary artery (RCA) 40 Left Circumflex Coronary artery (LCX) 97 Unknown

5.	Did this procedure require a re-exploration for bleeding? (R)	0 No 1 Yes, provide date: / / (2008-2020,DMY) 97 Unknown
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Labs (section title)

6.	Were any cardiac biomarkers elevated greater than 5 times the upper limit of normal within 24 hours following the procedure? (R)	0 No 1 Yes 97 Unknown
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Aspirin Therapy Post Index Hospitalization (Aspirin) (*form title/tab name*)**Aspirin Therapy Post Index Hospitalization** (*section title*)

1.	Has the subject taken any aspirin post index hospitalization? (<i>R</i>)	1	Yes
		96	No

Aspirin Therapy (*section title*)

	Total Daily Dose	Start Date	Stop Date
2.a			

Aspirin Therapy Entry (*section title*)

Total daily dose (<i>R</i>)	mg (<i>N9</i>)		
Start date (<i>R</i>)	/	/	(2008-2020, UMY)
Stop date (<i>R</i>)	90	/	/ (2008-2020, UMY)
	1	Ongoing	

Concomitant Medications (CM) (form title/tab name)

Concomitant Medications (section title)

1.	Did the subject take any medications, other than the study drug or aspirin, at any time from the informed consent date through the final visit/contact? (R)	1 Yes	93 No
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Concomitant Medications Report (section title)

	Sequence Number	Drug Name	Indication for Use	Start Date	Stop Date
2.a					
2.b					
2.c					

Concomitant Medications Report Entry (section title)

Sequence number (NR, HIDDEN, CALCULATED)	
Drug name (trade or generic name required) (R)	(A45)
Indication for Use? (R)	2 Prophylaxis or non-therapeutic 4 Adverse Event, specify E-code E (N5)
Start date (R)	/ / (1900-2020,UUY)

Stop date (R)	90 / / (2008-2020,UUY)
	1 Ongoing

Pre-Existing Conditions and Adverse Events (PCAE) (form title/tab name)

Event Code	Pre-Existing Condition/ Adverse Event	Onset Date	Onset Visit Number	Related to Study Drug	Related to Study Procedure	Con Med Started?	Stop Date	Severity	Event serious at anytime during the study?	Event Outcome	Has the severity of this event changed since the previous visit?	Adverse Event Reports		
												Date severity changed	Visit number of severity change	Severity
1.														
2.														
3.														

Ongoing Pre-Existing Conditions and Adverse Event Reports (section title)

	Event code (R)	E (N5) [Calculated]
1.	Pre-existing condition / Adverse event (R)	(A200)
2.	Onset date (R)	/ / (1900-2020,UUY)
3.	Onset visit number (R)	
4.	Related to study drug (R)	1 Yes 0 No
5.	Related to study procedure (R)	1 Yes 0 No
6.	Use of concomitant medication?(R)	1 Yes 0 No
7.	Stop date or continuing (R)	90 / / (2008-2020, UUY) 1 Continuing
8.	Severity (R)	1 Mild 2 Moderate 3 Severe
9.	Event serious at anytime during the study? (R,SV)	1 Yes 1 Death 2 Life-threatening 3 Disability 4 Hospitalization 5 Congenital Anomaly 8 Other 0 No
10.	Event outcome (R)	
11.	Has the severity of this event changed since the previous visit? (R)	1 Yes 0 No 99 Not applicable

Adverse Event Reports (section title)

	Date severity changed	Visit number of severity change	Severity
12.a			

Adverse Event Reports Entry (section title)

Date severity changed (R)	/ / (2008-2020,UUY)
Visit number of severity change (R)	
Severity (R)	1 Mild 2 Moderate 3 Severe

Pulldown List 1

<u>Value</u>	<u>Label</u>
1	Visit 1
2	Visit 2
3	Visit 3
4	Visit 4
5	Visit 5
6	Visit 6
7	Visit 7
8	Visit 8
9	Visit 9
10	Visit 10
11	Visit 11
12	Visit 12
13	Visit 13
14	Early Discontinuation
15	Final

Pulldown List 2

<u>Value</u>	<u>Label</u>
1	Recovered
2	Recovering/Resolving
3	Not Recovered
4	Recovered with sequelae
5	Fatal
97	Unknown

Medical Resource Utilization (MedRes) (form title/tab name)

Medical Resource Utilization (section title)

1.	Was the subject hospitalized? (R)	1	Yes
		93	No

Hospital Stay Data Reporting (section title)

	Hospital Tracking Number	Admission Date	Discharge Date	Type of Unit	Discharged alive?	Procedures performed in the hospital
2.a						

Hospital Stay Data Reporting Entry (section title)

Hospital Tracking Number (NR, CALCULATED)	H
Admission Date (R)	/ / (2008-2020, UMY)
Discharge Date (R)	90 / / (2008-2020, UMY)
	1 Ongoing
Type of Unit (R)	21 Acute Care #of ICU Nights #of CCU Nights #of Stepdown Care Nights #of Regular nights 15 Skilled Nursing Facility 39 Rehabilitation Facility 7 Nursing Home Facility (non skilled)

Was subject discharged alive? (R)	<div>1 Yes, discharged to:</div> <div>17 Home</div> <div>15 Skilled Nursing Facility</div> <div>Date admitted:</div> <div>/ / (2008-2020, UMY)</div> <div>Date discharged:</div> <div>90 / / (2008-2020, UMY)</div> <div>1 Ongoing</div> <div>39 Rehabilitation Facility</div> <div>Date admitted:</div> <div>/ / (2008-2020, UMY)</div> <div>Date discharged:</div> <div>90 / / (2008-2020, UMY)</div> <div>1 Ongoing</div> <div>7 Nursing Home Facility (non-skilled)</div> <div>Date admitted:</div> <div>/ / (2008-2020, UMY)</div> <div>Date discharged:</div> <div>90 / / (2008-2020, UMY)</div> <div>1 Ongoing</div> <div>11 Another Hospital</div> <div>96 No</div>
Procedures performed in the hospital (R)	<div>1 Check all that apply:</div> <div>182 Coronary CT angiography</div> <div>254 Vascular surgical repair</div> <div>380 Peripheral angiography</div> <div>301 Peripheral vascular intervention</div> <div>296 Carotid stent</div> <div>297 Carotid endarterectomy</div> <div>294 Electrophysiologic (EP) Study</div> <div>295 Permanent pacemaker</div> <div>299 ICD</div> <div>95 None of the above</div>

Outpatient Resource (section title)

3. Did the subject have any outpatient visits? (R)	<div>1 Yes</div> <div>0 No</div>
--	----------------------------------

Outpatient Resource Reporting (section title)

	Date of the Outpatient Visit	Outpatient procedures performed
4.a		

Outpatient Resource Reporting Entry (section title)

Date of the outpatient visit (R)	90 / / (2008-2020, UMY)
	97 Unknown
Outpatient procedures performed? (R)	1 Check all that apply: 182 Coronary CT angiography 254 Vascular surgical repair 380 Peripheral angiography 301 Peripheral vascular intervention 296 Carotid stent 297 Carotid endarterectomy 294 Electrophysiologic (EP) Study 295 Permanent pacemaker 299 ICD 95 None of the above

Emergency Room Visit (section title)

5. Did the subject visit the emergency room but was not hospitalized? (R)	1 Yes
	0 No

Emergency Room Visit Reporting (section title)

	Emergency Room visit date
6.a	

Emergency Room Visit Reporting Entry (section title)

Date of emergency room visit (R)	/ / (2008-2020, UMY)
----------------------------------	----------------------

CEC Trigger (CECTrig) *(form title/tab name)*
CEC Trigger report *(section title)*

1.	Did the subject die? <i>(R, SV)</i>	0 No 1 Yes 97 Unknown
2.	Did a Myocardial Infarction (MI) occur? <i>(R, SV)</i>	0 No 1 Yes 97 Unknown
3.	Was the subject rehospitalized for recurrent unstable angina (UA)? <i>(R, SV)</i>	0 No 1 Yes 97 Unknown
4.	Did the subject experience a stroke? <i>(R, SV)</i>	0 No 1 Yes 97 Unknown
5.	Was a stent thrombosis identified? <i>(R, SV)</i>	0 No 1 Yes 97 Unknown

6.	Did the subject experience a bleeding event? NOTE: If the bleed event is a hemorrhagic stroke, intracranial bleed or subdural hematoma with new neurological signs/symptoms consistent with a stroke, answer this question as "No" and complete only the Stroke Endpoint eCRF. (R, SV)	0	No
		1	Yes
		97	Unknown

Endpoint Reporting: Death (Death Endpoint) *(form title/tab name)*

Endpoint Reporting: Death *(section title)*

1.	Adverse Event code of primary cause of death <i>(R,SV)</i>	E <i>(N5)</i>
	CEC tracking number <i>(R,SV)</i>	<i>(A18) [Calculated]</i>
2.	Hospital Tracking Number <i>(R,SV)</i>	90 H <i>(A5)</i> 96 Not applicable
3.	Date and time of death <i>(R,SV)</i>	/ / <i>(2008-2020, UMYUU)</i> :
4.	Primary cause of death <i>(R,SV)</i>	4 Cardiovascular 3 Non-Cardiovascular 97 Unknown
5.	Narrative of event <i>(R,SV)</i>	<i>(A2000)</i>
6.	Date that all available source documentation sent by site <i>(R)</i>	90 / / <i>(2008-2020, DMY)</i> 97 Source document information requested are not available and cannot be obtained

Location of Death *(section title)*

7.	Where did the subject die? (R, SV)	17	Home
		11	Hospital
		2	Emergency Room
		7	Nursing Home
		12	Other Care Facility
		15	Skilled Nursing Facility
		99	Other

Autopsy Reporting *(section title)*

8.	Was an autopsy performed? (R,SV)	0	No
		1	Yes

CEC Use Only *(section title)*

9.	Was this a CEC-triggered event? [for office use only] (NR)	0	No
		1	Yes

Death: CEC Tracking report *(section title)*

10.	CEC Tracking Number (NR) <i>(mapped from Death section)</i>	(A18)	
11.	Status (NR)		
12.	Date CEC packet sent to Phase I (NR)	/	/ (2008-2020,DMY)
13.	Reviewer #1 (NR)		
14.	Date CEC packet returned from first reviewer (NR)	/	/ (2008-2020,DMY)
15.	Reviewer #2 (NR)		
16.	Date CEC packet returned from second reviewer (NR)	/	/ (2008-2020,DMY)
17.	Full committee review (NR)	1	Yes
18.	Date sent to full committee (NR)	/	/ (2008-2020,DMY)
19.	Re-review needed (NR)	1	Yes
20.	Type of re-review (NR)		
21.	Date of re-review (NR)	/	/ (2008-2020,DMY)

22.	Comments <i>(NR)</i>	(A200)	
23.	Date source documentation received by CEC <i>(NR)</i>	/	/ (2008-2020,DMY)

Death Adjudication *(section title)*

24.	CEC Tracking Number <i>(NR) (mapped from Death section)</i>	(A18)	
25.	Did death occur? <i>(NR)</i>	0	No
		1	Yes, provide date and time: / / : (2008-2020, UMYUU)
26.	Primary cause of death <i>(NR)</i>	4	Cardiovascular 2169 Congestive Heart Failure 1598 Cardiogenic Shock 2335 Cardiac Rupture 1047 Myocardial Infarction 2297 Dysrhythmia 2303 Stent Thrombosis 1678 Directly related to Revascularization (CABG or PCI) 2299 Intracranial hemorrhage 1977 Non-Hemorrhagic stroke 1963 Sudden death 1479 Pulmonary Embolism 1975 Stroke, unknown type 97 Unknown 99 Other
		3	Non-Cardiovascular 1972 Accidental 1754 Trauma 730 Hemorrhage, not intracranial 2129 Infection 1968 Malignancy 1973 Suicide 99 Other

Pulldown List 1

<u>Value</u>	<u>Label</u>
1	Congestive Heart Failure [2169]
2	Cardiogenic Shock [1598]
3	Cardiac rupture [2335]
4	Myocardial Infarction [1047]
5	Dysrhythmia [2297]
6	Stent Thrombosis [2303]
7	Directly related to Revascularization (CABG or PCI) [1678]
8	Intracranial hemorrhage [2299]
9	Non-Hemorrhagic stroke [1977]
10	Sudden Death [1963]
11	Pulmonary embolism [1479]
12	Stroke, unknown type [1975]
99	Other

Pulldown List 2	
<u>Value</u>	<u>Label</u>
1	Accidental [1972]
2	Trauma [1754]
3	Hemorrhage, not intracranial [730]
4	Infection [2129]
5	Malignancy [1968]
6	Suicide [1973]
99	Other

Pulldown List 3	
<u>Value</u>	<u>Label</u>
1	New
2	Outstanding source documents
3	Phase I Review

4	Committee Review (Phase II)
5	Resolved/completed
6	No action needed
7	Hold
8	Re-review

Pulldown List 4	
Value	Label
1	Reviewer 1
2	Reviewer 2
3	Reviewer 3
4	Reviewer 4
5	Reviewer 5
6	Reviewer 6
7	Reviewer 7
8	Reviewer 8
9	Reviewer 9
10	Reviewer 10
11	Reviewer 11
12	Reviewer 12
13	Reviewer 13
14	Reviewer 14
15	Reviewer 15
16	Reviewer 16
17	Reviewer 17
18	Reviewer 18
19	Reviewer 19
20	Reviewer 20

Pulldown List 5	
Value	Label
1	Random QC
2	Data Change
3	Additional Data Received
4	Other

Endpoint Reporting: Bleeding (Bleeding Endpoint) *(form title/tab name)*

Adverse Event code	CEC tracking number	Date and time of event	Location/type of bleed	Provocation of bleeding event	Narrative of event	Date source documentation sent by site	If provocation of bleeding event was procedure-related, please specify the procedure.	Was a CT performed?	Was an MRI performed?	Was an ultrasound performed?	Was an endoscopy performed?	Select all items that are relevant to this bleed	Hemoglobin/Hematocrit reporting			Was this a CEC-triggered event? [for office use only]
													Date and time	Hemoglobin Result	Hematocrit Result	
1.																
2.																

CEC Tracking Number	Status	Date CEC packet sent to Phase I	Reviewer #1	Date CEC packet returned from first reviewer	Reviewer #2	Date CEC packet returned from second reviewer	Full committee review	Date sent to full committee	Re-review needed	Type of re-review	Date of re-review	Comments	Date source documentation received by CEC

CEC Tracking Number	Did a bleeding event occur?	Date and time of onset of event	Was the bleed CABG-related?	Was the bleed life-threatening?	Primary bleeding event location?	TIMI Bleeding Classification

Endpoint Reporting: Bleeding *(section title)*

Note: Suspected Hemorrhagic Stroke or intracranial bleeding should be recorded only on the Stroke Endpoint form.

Note: Subdural hematomas that DO NOT have new neurological signs and symptoms consistent with a stroke should be reported as a bleed only.

1.	Adverse Event code <i>(R,SV)</i>	E <i>(N5)</i>
	CEC tracking number <i>(R,SV)</i>	<i>(A18) [Calculated]</i>

2.	Date and time of event <i>(R,SV)</i>	/ / : (2008-2020, UMYUU)
3.	Location/type of bleed <i>(R,SV)</i>	208 Epistaxis 448 Gastrointestinal 347 Hematuria 226 Pericardial 402 Hemoptysis 449 Intraocular 353 Vascular access site 256 Retroperitoneal 492 Surgical incision site 183 Subdural hematoma 44 Breast 349 Vaginal 345 Urethral 99 Other If 'Other' then, specify (A50)
4.	Provocation of bleeding event <i>(R,SV)</i>	739 Procedure-related 2313 Spontaneous 2314 Trauma
5.	Narrative of event <i>(R,SV)</i>	(A2000)
6.	Date source documentation sent by site <i>(R)</i>	90 / / (2008-2020, DMY) 97 Source document information requested are not available and cannot be obtained 99 Not applicable

Endpoint Reporting: Bleeding Procedures *(section title)*

7.	If provocation of bleeding event was procedure-related, please specify the procedure. <i>(NR,SV)</i>	180 Percutaneous Coronary Intervention (PCI) 179 Coronary Artery Bypass Graft surgery (CABG) 99 Other procedure
8.	Was a CT performed? <i>(R,SV)</i>	0 No 1 Yes
9.	Was an MRI performed? <i>(R,SV)</i>	0 No 1 Yes
10.	Was an ultrasound performed? <i>(R,SV)</i>	0 No 1 Yes

11.	Was an endoscopy performed? (R,SV)	0	No
		1	Yes

Endpoint Reporting: Bleeding Hemorrhage Criteria (section title)

12.	Select all items that are relevant to this bleed (R,SV)	1	Check all that apply:
		2	Clinically overt bleeding associated with a fall in hemoglobin
		8	Fatal
		6	Hypotension that required treatment with intravenous inotropic agents
		10	Hospitalization or prolongation of hospitalization
		H	(N5)
		5	Required laboratory evaluation
		3	Required medical treatment
		4	Required surgical treatment
		7	Required transfusion
		95	None of the above

Hemoglobin/Hematocrit reporting (section title)

Note: Record all values for every clinically overt bleed.			
	Date and Time	Hemoglobin Result	Hematocrit Result
13.a			

Hemoglobin/Hematocrit reporting Entry (section title)

Note: Record all values for every clinically overt bleed.			
Date and time (R,SV)	90	/	/
		:	(2008-2020,DMYHM)
	93	Not done	
Hemoglobin (R,SV)	90	Result (N9.0)	
	93	Not done	
Hematocrit (R,SV)	90	Result (N9.0)	
	93	Not done	

CEC Use Only (section title)

14.	Was this a CEC-triggered event? <i>[for office use only] (NR)</i>	0 No 1 Yes
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Bleed: CEC Tracking report *(section title)*

15.	CEC Tracking Number <i>(NR)</i>	(A18)
16.	Status <i>(NR)</i>	
17.	Date CEC packet sent to Phase I <i>(NR)</i>	/ / (2008-2020,DMY)
18.	Reviewer #1 <i>(NR)</i>	
19.	Date CEC packet returned from first reviewer <i>(NR)</i>	/ / (2008-2020,DMY)
20.	Reviewer #2 <i>(NR)</i>	
21.	Date CEC packet returned from second reviewer <i>(NR)</i>	/ / (2008-2020,DMY)
22.	Full committee review <i>(NR)</i>	1 Yes
23.	Date sent to full committee <i>(NR)</i>	/ / (2008-2020,DMY)
24.	Re-review needed <i>(NR)</i>	1 Yes
25.	Type of re-review <i>(NR)</i>	
26.	Date of re-review <i>(NR)</i>	/ / (2008-2020,DMY)
27.	Comments <i>(NR)</i>	(A200)
28.	Date source documentation received by CEC <i>(NR)</i>	/ / (2008-2020,DMY)

Bleeding Adjudication *(section title)*

29.	CEC Tracking Number <i>(NR)</i>	(A18)
30.	Did a bleeding event occur? <i>(NR)</i>	0 No 1 Yes
31.	Date and time of onset of event <i>(NR)</i>	/ / (2008-2020,UMYUU) :
32.	Was the bleed CABG-related? <i>(NR)</i>	0 No 1 Yes
33.	Was the bleed life-threatening? <i>(NR)</i>	0 No 1 Yes

34.	Primary bleeding event location? (NR)	<div>208 Epistaxis</div> <div>448 Gastrointestinal</div> <div>347 Hematuria</div> <div>226 Pericardial</div> <div>402 Hemoptysis</div> <div>449 Intraocular</div> <div>353 Vascular access site</div> <div>256 Retroperitoneal</div> <div>492 Surgical incision site</div> <div>183 Subdural hematoma</div> <div>95 No site identified</div> <div>44 Breast</div> <div>349 Vaginal</div> <div>345 Urethral</div> <div>99 Other If 'Other' then, specify (A50)</div>
35.	TIMI Bleeding Classification (NR)	<div>93 Adjudicated but did not meet TIMI criteria</div> <div>1 TIMI major</div> <div>3 TIMI minor</div> <div>4 TIMI minimal</div>

Pulldown List 1	
Value	Label
111	g/dl
32	g%
31	g/l
391	mmol/L

Pulldown List 2	
Value	Label
680	%
679	Decimal
627	L/L

Pulldown List 3	
Value	Label
1	New
2	Outstanding source documents
3	Phase I Review

4	Committee Review (Phase II)
5	Resolved/completed
6	No action needed
7	Hold
8	Re-review

Pulldown List 4	
Value	Label
1	Reviewer 1
2	Reviewer 2
3	Reviewer 3
4	Reviewer 4
5	Reviewer 5
6	Reviewer 6
7	Reviewer 7
8	Reviewer 8
9	Reviewer 9
10	Reviewer 10
11	Reviewer 11
12	Reviewer 12
13	Reviewer 13
14	Reviewer 14
15	Reviewer 15
16	Reviewer 16
17	Reviewer 17
18	Reviewer 18
19	Reviewer 19
20	Reviewer 20

Pulldown List 5	
Value	Label
1	Random QC
2	Data Change
3	Additional Data Received
4	Other

Endpoint Reporting: Stroke (Stroke Endpoint) *(form title/tab name)*

Adverse Event code	CEC tracking number	Date and time of onset of event	Was this a new, persistent, neurological deficit of rapid onset that lasted more than 24 hours?	What type of stroke event occurred?	Narrative of event	Date source documentation sent by site	Was a CT performed?	Was an MRI performed?	Was a brain autopsy performed?	Was the subject hospitalized for this event?	Was this a CEC-triggered event? [for office use only]
1.											

Endpoint Reporting: Stroke *(section title)*

NOTE: All suspected hemorrhagic strokes, intracranial bleeds, or subdural hematomas with new neurological signs and symptoms consistent with a stroke should be reported as a stroke only.

1.	Adverse Event code <i>(R,SV)</i>	E <i>(N5)</i>
	CEC tracking number <i>(R,SV)</i>	<i>(A18) [Calculated]</i>
2.	Date and time of onset of event <i>(R,SV)</i>	/ / <i>(2008-2020,DMYUU)</i> :
3.	Was this a new, persistent, neurological deficit of rapid onset that lasted more than 24 hours? <i>(R,SV)</i>	0 No 1 Yes 97 Unknown

4.	What type of stroke event occurred? (R,SV)	10 Ischemic (Non-hemorrhagic) 9 Hemorrhagic 3 Ischemic with Hemorrhagic Conversion 97 Uncertain
5.	Narrative of event (R,SV)	(A2000)
6.	Date source documentation sent by site (R)	90 / / (2008-2020,DMY) 97 Source document information requested are not available and cannot be obtained

Endpoint Reporting: Stroke Procedures (section title)

7.	Was a CT performed? (R,SV)	96 No 1 Yes
8.	Was an MRI performed? (R,SV)	96 No 1 Yes
9.	Was a brain autopsy performed? (R,SV)	96 No 1 Yes

Endpoint Reporting: Stroke Hospitalization (section title)

10.	Was the subject hospitalized for this event? (R,SV)	0 No 1 Yes, provide hospitalization tracking number: H (N5)
-----	---	---

CEC Use Only (section title)

11.	Was this a CEC-triggered event? [for office use only] (NR)	0 No 1 Yes
-----	--	---------------

Stroke: CEC Tracking report (section title)

12.	CEC Tracking Number (NR)	(A18)
13.	Status (NR)	
14.	Date CEC packet sent to Phase I (NR)	/ / (2008-2020,DMY)
15.	Reviewer #1 (NR)	
16.	Date CEC packet returned from first reviewer (NR)	/ / (2008-2020,DMY)
17.	Reviewer #2 (NR)	
18.	Date CEC packet returned from second reviewer (NR)	/ / (2008-2020,DMY)
19.	Full committee review (NR)	1 Yes
20.	Date sent to full committee (NR)	/ / (2008-2020,DMY)
21.	Re-review needed (NR)	1 Yes
22.	Type of re-review (NR)	
23.	Date of re-review (NR)	/ / (2008-2020,DMY)
24.	Comments (NR)	(A200)
25.	Date source documentation received by CEC (NR)	/ / (2008-2020,DMY)

Stroke Adjudication *(section title)*

26.	CEC Tracking Number <i>(NR)</i>	(A18)
27.	Did the subject have a stroke? <i>(NR)</i>	0 No 1 Yes
28.	Date and time of onset of event <i>(NR)</i>	/ / : (2008-2020,DMYUU)
29.	Type of stroke? <i>(NR)</i>	9 Primary Hemorrhagic 7 Intraparenchymal hemorrhage 8 Subdural Hematoma 11 Intraventricular Hemorrhage 2 Subarachnoid Hemorrhage 10 Ischemic (Non-hemorrhagic) 3 Ischemic with Hemorrhagic Conversion 97 Uncertain
30.	If the stroke was hemorrhagic, provide the provocation of the bleeding event.	739 Procedure-related 2313 Spontaneous 2314 Trauma

Pulldown List 1

<u>Value</u>	<u>Label</u>
1	New
2	Outstanding source documents
3	Phase I Review
4	Committee Review (Phase II)
5	Resolved/completed
6	No action needed
7	Hold

8	Re-review
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Pulldown List 2	
Value	Label
1	Reviewer 1
2	Reviewer 2
3	Reviewer 3
4	Reviewer 4
5	Reviewer 5
6	Reviewer 6
7	Reviewer 7
8	Reviewer 8
9	Reviewer 9
10	Reviewer 10
11	Reviewer 11
12	Reviewer 12
13	Reviewer 13
14	Reviewer 14
15	Reviewer 15
16	Reviewer 16
17	Reviewer 17
18	Reviewer 18
19	Reviewer 19
20	Reviewer 20

Pulldown List 3	

<u>Value</u>	<u>Label</u>
1	Random QC
2	Data Change
3	Additional Data Received
4	Other

Endpoint Reporting: Severe Recurrent Ischemia (Ischemia Endpoint) *(form title/tab name)*

Adverse Event code	CEC tracking number	Was the subject initially admitted to the hospital for this event?	If subject was hospitalized at the time of the event, was hospitalization prolonged as a result of this event?	Was a PCI performed within 24 hours prior to the event?	Was a CABG performed within 24 hours prior to the event?	Narrative of event	Date source documentation sent by site	Date and time of symptom onset?	Adverse Event onset date	Maximum duration of symptoms at rest associated with this event	Was a Percutaneous Coronary Intervention (PCI) performed as a result of this event?	Was a Coronary Artery Bypass Graft surgery (CABG) performed as a result of this event?	Were ECGs performed?	Was the event caused by stent thrombosis?	Were cardiac biomarkers assessed for this event?	Cardiac Biomarkers (CK,CK-MB,TROPONIN)					Was this a CEC-triggered event? [for office use only]
																Date and time of biomarker panel drawn	CK Result	CK-MB Result	Troponin I Result	Troponin T Result	
1.																					
2.																					

CEC tracking number	Status	Date CEC packet sent to Phase I	Reviewer #1	Date CEC packet returned from first reviewer	Reviewer #2	Date CEC packet returned from second reviewer	Full committee review	Date sent to full committee	Re-review needed	Type of re-review	Date of re-review	Comments	Date source documentation received by CEC
1.													
2.													

CEC tracking number	Did MI occur?	Type of MI	Was this MI related to a procedure?	Cardiac biomarkers assessed	Did rehospitalization for recurrent unstable angina occur?	Did new ST-segment depression occur in at least two or more leads?	Was an unplanned revascularization procedure performed as a result of this event?
1.							
2.							

Endpoint Reporting: Severe Recurrent Ischemia *(section title)*

MI or Re-hospitalization for unstable angina will be recorded on this form.		
1.	Adverse Event code (R,SV)	E (N5)
	CEC tracking number (R,SV)	(A18) [Calculated]
2.	Was the subject initially admitted to the hospital for this event? (R,SV)	0 No 1 Yes, Hospitalization tracking number H (N5) Date of hospital admission / / (2008-2020,DMY) Date of hospital discharge / / (2008-2020,UUU)
3.	If subject was hospitalized at the time of the event, was hospitalization prolonged as a result of this event? (R,SV)	0 No 1 Yes, Hospitalization tracking number H (N5) Date of first evaluation for this event / / (2008-2020,DMY) 96 Not applicable
4.	Was a PCI performed within 24 hours prior to the event? (R,SV)	0 No 1 Yes
5.	Was a CABG performed within 24 hours prior to the event? (R,SV)	0 No 1 Yes
6.	Narrative of event (R,SV)	(A2000)
7.	Date all available source documentation sent by site (R)	90 / / (2008-2020,DMY) 97 Source document information requested are not available and cannot be obtained

Symptom Onset (section title)

8.	Date and time of symptom onset? (R,SV)	90 / / : (2008-2020,DMYUU) 95 No symptoms occurred 97 Unknown
9.	Adverse Event onset date (R,SV)	/ / (1900-2020,UUY)
10.	Maximum duration of symptoms at rest associated with this event (R,SV)	90 # minutes (N5) 95 No symptoms occurred 97 Unknown

Procedures (section title)

11.	Was a Percutaneous Coronary Intervention (PCI) performed as a result of this event? (R,SV)	0 No 1 Yes
12.	Was a Coronary Artery Bypass Graft surgery (CABG) performed as a result of this event? (R,SV)	0 No 1 Yes
13.	Were ECGs performed? (R,SV)	0 No 1 Yes

Diagnosis (section title)

14.	Was the event caused by stent thrombosis? (R,SV)	0 No 1 Yes
-----	--	---------------

Cardiac Biomarkers (CK,CK-MB,TROPONIN) (section title)

15.	Were cardiac biomarkers assessed for this event? (R,SV)	0 No
		1 Yes

Cardiac Biomarkers (CK,CK-MB,TROPONIN) (section title)

Note: Record all biomarker results for severe recurrent ischemia event					
	Date and time of biomarker panel drawn	CK Result	CK-MB Result	Troponin I Result	Troponin T Result
16.a					

Cardiac Biomarkers (CK,CK-MB,TROPONIN) Entry (section title)

Note: Record all biomarker results for severe recurrent ischemia event		
Date and time of biomarker panel drawn (R,SV)	/ / : (2008-2020,DMYUJ)	
CK (R,SV)	1 Result (N9.0) Upper Limit of Normal (N9.0) If 'Other' then specify (A50)	93 Not done
CK-MB (R,SV)	1 Result (N9.0) Upper Limit of Normal (N9.0) If 'Other' then specify (A50)	93 Not done
Troponin I (R,SV)	1 Result (N9.0) Upper Limit of Normal (N9.0) If 'Other' then specify (A50)	93 Not done
Troponin T (R,SV)	1 Result (N9.0) Upper Limit of Normal (N9.0) If 'Other' then specify (A50)	93 Not done

CEC Use Only (section title)

17.	Was this a CEC-triggered event? [for office use only] (NR)	0 No
		1 Yes

Severe Recurrent Ischemia: CEC Tracking report (section title)

18.	CEC Tracking Number (NR)	(A18)
19.	Status (NR)	
20.	Date CEC packet sent to Phase I (NR)	/ / (2008-2020,DMY)
21.	Reviewer #1 (NR)	
22.	Date CEC packet returned from first reviewer (NR)	/ / (2008-2020,DMY)
23.	Reviewer #2 (NR)	
24.	Date CEC packet returned from second reviewer (NR)	/ / (2008-2020,DMY)

25.	Full committee review <i>(NR)</i>	1 Yes
26.	Date sent to full committee <i>(NR)</i>	/ / <i>(2008-2020,DMY)</i>
27.	Re-review needed <i>(NR)</i>	1 Yes
28.	Type of re-review <i>(NR)</i>	
29.	Date of re-review <i>(NR)</i>	/ / <i>(2008-2020,DMY)</i>
30.	Comments <i>(NR)</i>	<i>(A200)</i>
31.	Date source documentation received by CEC <i>(NR)</i>	/ / <i>(2008-2020,DMY)</i>

Severe Recurrent Ischemia Adjudication (Myocardial Infarction (MI)) *(section title)*

32.	CEC Tracking Number <i>(NR)</i>	<i>(A18)</i>
33.	Did MI occur? <i>(NR)</i>	0 No 1 Yes / / : <i>(2008-2020,DMYUU)</i>
34.	Type of MI <i>(NR)</i>	2304 STEMI 2305 NSTEMI 1499 Q-wave
35.	Was this MI related to a procedure? <i>(NR)</i>	1 Yes 180 PCI 179 CABG 0 No, spontaneous
36.	Cardiac biomarkers assessed <i>(NR)</i>	1 Peak CK 1 result <i>(N9.0)</i> ULN <i>(N9.0)</i> 93 Not done 2 Peak CK-MB 1 result <i>(N9.0)</i> ULN <i>(N9.0)</i> 93 Not done 3 Peak Troponin I 1 result <i>(N9.0)</i> ULN <i>(N9.0)</i> 93 Not done 4 Peak Troponin T 1 result <i>(N9.0)</i> ULN <i>(N9.0)</i> 93 Not done

Severe Recurrent Ischemia Adjudication (Rehospitalization for Recurrent Unstable Angina) *(section title)*

37.	Did rehospitalization for recurrent unstable angina occur? <i>(NR)</i>	0 No 1 Yes / / : <i>(2008-2020,DMYUU)</i>
38.	Did new ST-segment depression occur in at least two or more leads? <i>(NR)</i>	0 No 1 Yes 97 Unknown
39.	Was an unplanned revascularization procedure performed as a result of this event? <i>(NR)</i>	0 No 1 Yes

Pulldown List 1	
Value	Label

111	ug/L
153	ng/mL
231	U/L
311	IU/L
253	mU/mL
333	mIU/mL
202	uKat/L
99	Other

Pulldown List 2	
Value	Label
1	New
2	Outstanding source documents
3	Phase I Review
4	Committee Review (Phase II)
5	Resolved/completed
6	No action needed
7	Hold
8	Re-review

Pulldown List 3	
Value	Label
1	Reviewer 1
2	Reviewer 2
3	Reviewer 3
4	Reviewer 4
5	Reviewer 5
6	Reviewer 6
7	Reviewer 7
8	Reviewer 8
9	Reviewer 9
10	Reviewer 10
11	Reviewer 11
12	Reviewer 12
13	Reviewer 13
14	Reviewer 14
15	Reviewer 15
16	Reviewer 16
17	Reviewer 17
18	Reviewer 18
19	Reviewer 19
20	Reviewer 20

Pulldown List 4	
Value	Label
1	Random QC
2	Data Change
3	Additional Data Received
4	Other

Endpoint Reporting: Stent Thrombosis (Stent Endpoint) *(form title/tab name)*

Adverse Event code	CEC tracking number	Hospitalization tracking number	Date and time of event	Narrative of event	Date all available source documentation sent by site	Was Aspirin discontinued between stent implantation and time of the stent thrombosis event?	Was study drug discontinued prior to the time of the stent thrombosis event?	If study drug was discontinued, did the subject receive open-label thienopyridine prior to the stent thrombosis?	If the subject received open-label thienopyridine, did the subject discontinue open-label thienopyridine prior to the timing of the stent thrombosis event?	Did the stent thrombosis result in any of the following procedures?	When was the thrombosed stent initially implanted?	Did stent thrombosis result in any of the following outcomes?	Was this a CEC-triggered event? [for office use only]
1.													
2.													
3.													

CEC tracking number	Status	Date CEC packet sent to Phase I	Reviewer #1	Date CEC packet returned from first reviewer	Reviewer #2	Date CEC packet returned from second reviewer	Full committee review	Date sent to full committee	Re-review needed	Type of re-review	Date of re-review	Comments	Date source documentation received by CEC
1.													
2.													
3.													

CEC tracking number	Did stent thrombosis occur?	Date of implantation of thrombosed stent:	Type of thrombosed stent	Classification of stent thrombosis?	Vessel type	Vessel location of thrombosed stent	Vessel diameter	Total length of vessel stented	Minimum stent diameter	Was there use of IVUS guidance?	Maximum post stent deployment balloon inflation pressure	Diameter of balloon used for post stent dilatation	Length of balloon used for post stent dilatation	Thrombosis at a bifurcation lesion	Were overlapping stents involved with the stent thrombosis?
1.															
2.															
3.															

Endpoint Reporting: Stent Thrombosis (section title)

1.	Adverse Event code (R,SV)	E (N5)
	CEC tracking number (R,SV)	(A18) [Calculated]
2.	Hospitalization tracking number (R,SV)	H (N5)
3.	Date and time of event (R,SV)	/ / : (2008-2020,DMYUU)
4.	Narrative of event (R,SV)	(A2000)
5.	Date all available source documentation sent by site (R)	90 / / (2008-2020,DMY) 97 Source document information requested are not available and cannot be obtained

Anti-platelet medications (section title)

6.	Was Aspirin discontinued between stent implantation and time of the stent thrombosis event? (R,SV)	0 No 1 Yes 93 Not applicable
7.	Was study drug discontinued prior to the time of the stent thrombosis event? (R,SV)	0 No 1 Yes

8.	If study drug was discontinued, did the subject receive open-label thienopyridine prior to the stent thrombosis? <i>(NR,SV)</i>	0 No 1 Yes
9.	If the subject received open-label thienopyridine, did the subject discontinue open-label thienopyridine prior to the timing of the stent thrombosis event? <i>(NR,SV)</i>	0 No 1 Yes

Procedures *(section title)*

10.	Did the stent thrombosis result in any of the following procedures? <i>(R,SV)</i>	1 If Yes, check all that apply: 180 PCI 179 CABG 95 None of the above
11.	When was the thrombosed stent initially implanted? <i>(R,SV)</i>	90 / / <i>(1900-2020,UUY)</i> 97 Unknown

Diagnosis *(section title)*

12.	Did stent thrombosis result in any of the following outcomes? <i>(R,SV)</i>	1 If Yes, check all that apply: 2370 CV Death 2316 Severe Recurrent Ischemia 95 None of the above
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CEC Use Only *(section title)*

13.	Was this a CEC-triggered event? <i>[for office use only] (NR)</i>	0 No 1 Yes
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Stent: CEC Tracking report *(section title)*

14.	CEC Tracking Number <i>(NR)</i>	<i>(A18)</i>
15.	Status <i>(NR)</i>	
16.	Date CEC packet sent to Phase I <i>(NR)</i>	/ / <i>(2008-2020,DMY)</i>
17.	Reviewer #1 <i>(NR)</i>	
18.	Date CEC packet returned from first reviewer <i>(NR)</i>	/ / <i>(2008-2020,DMY)</i>
19.	Reviewer #2 <i>(NR)</i>	
20.	Date CEC packet returned from second reviewer <i>(NR)</i>	/ / <i>(2008-2020,DMY)</i>
21.	Full committee review <i>(NR)</i>	1 Yes
22.	Date sent to full committee <i>(NR)</i>	/ / <i>(2008-2020,DMY)</i>
23.	Re-review needed <i>(NR)</i>	1 Yes

24.	Type of re-review <i>(NR)</i>	
25.	Date of re-review <i>(NR)</i>	/ / <i>(2008-2020,DMY)</i>
26.	Comments <i>(NR)</i>	<i>(A200)</i>
27.	Date source documentation received by CEC <i>(NR)</i>	/ / <i>(2008-2020,DMY)</i>

Stent Thrombosis Adjudication *(section title)*

28.	CEC Tracking Number <i>(NR)</i>	<i>(A18)</i>
29.	Did stent thrombosis occur? <i>(NR)</i>	0 No 1 Yes / / : <i>(2008-2020,DMYUU)</i>
30.	Date of implantation of thrombosed stent: <i>(NR)</i>	90 / / <i>(1900-2020,UUY)</i> 97 Unknown
31.	Type of thrombosed stent: <i>(NR)</i>	79 DES 77 BMS 144 DES and BMS 99 Other 97 Unknown
32.	Classification of stent thrombosis? <i>(NR)</i>	1 Definite stent thrombosis 2 Angiographic confirmation 4 Occlusive thrombus 3 Non-occlusive thrombus 5 Pathological confirmation 6 Probable stent thrombosis 7 Possible stent thrombosis
33.	Vessel type <i>(NR)</i>	490 Native coronary artery 489 Saphenous vein bypass graft 13 Arterial bypass graft 97 Unknown
34.	Vessel location of thrombosed stent <i>(NR)</i>	
35.	Vessel diameter <i>(NR)</i>	1 mm <i>(N11.1)</i> 97 Unknown
36.	Total length of vessel stented <i>(NR)</i>	1 <=20 mm 2 21-30 mm 3 31-40 mm 4 >40 mm 97 Unknown
37.	Minimum stent diameter <i>(NR)</i>	1 mm <i>(N11.1)</i> 97 Unknown

38.	Was there use of IVUS guidance? <i>(NR)</i>	<div>0 No</div> <div>1 Yes</div> <div>97 Unknown</div>
39.	Maximum post stent deployment balloon inflation pressure <i>(NR)</i>	<div>1 atmospheres <i>(N9.0)</i></div> <div>97 Unknown</div>
40.	Diameter of balloon used for post stent dilatation <i>(NR)</i>	<div>1 mm <i>(N11.1)</i></div> <div>97 Unknown</div>
41.	Length of balloon used for post stent dilatation <i>(NR)</i>	<div>1 mm <i>(N11.1)</i></div> <div>97 Unknown</div>
42.	Thrombosis at a bifurcation lesion <i>(NR)</i>	<div>0 No</div> <div>1 Yes</div> <div>97 Unknown</div>
43.	Were overlapping stents involved with the stent thrombosis? <i>(NR)</i>	<div>0 No</div> <div>1 Yes</div> <div>97 Unknown</div>

Pulldown List 1	
Value	Label
1	New
2	Outstanding source documents
3	Phase I Review
4	Committee Review (Phase II)
5	Resolved/completed
6	No action needed
7	Hold
8	Re-review

Pulldown List 2	
Value	Label
1	Reviewer 1
2	Reviewer 2
3	Reviewer 3
4	Reviewer 4
5	Reviewer 5
6	Reviewer 6
7	Reviewer 7
8	Reviewer 8
9	Reviewer 9

10	Reviewer 10
11	Reviewer 11
12	Reviewer 12
13	Reviewer 13
14	Reviewer 14
15	Reviewer 15
16	Reviewer 16
17	Reviewer 17
18	Reviewer 18
19	Reviewer 19
20	Reviewer 20

Pulldown List 3	
Value	Label
1	Random QC
2	Data Change
3	Additional Data Received
4	Other

Pulldown List 4	
Value	Label
1	1, Proximal right coronary artery conduit segment
2	2, Mid-right coronary artery conduit segment
3	3, Distal right coronary artery conduit segment
4	4, Right posterior descending artery segment
5	5, Right posterior atrioventricular segment
6	6, First right posterolateral segment
7	7, Second right posterolateral segment
8	8, Third right posterolateral segment
9	9, Posterior descending septal perforators segment
10	10, Acute marginal segment (s)
11	11, Left main coronary artery segment
12	12, Proximal LAD artery segment
13	13, Mid-LAD artery segment
14	14, Distal LAD artery segment
15	15, First diagonal branch segment
16	15a, Lateral first diagonal branch segment
17	16, Second diagonal branch segment
18	16a, Lateral second diagonal branch segment

19	17, LAD septal perforators segment
20	18, Proximal circumflex artery segment
21	19, Mid-circumflex artery segment
22	19a, Distal circumflex artery segment
23	20, First obtuse marginal branch segment
24	20a, Lateral first obtuse marginal branch segment
25	21, Second obtuse marginal branch segment
26	21a, Lateral second obtuse marginal branch segment
27	22, Third obtuse marginal branch segment
28	22a, Lateral third obtuse marginal branch segment
29	23, Circumflex artery AV groove continuation segment
30	24, First left posterolateral branch segment
31	25, Second left posterolateral branch segment
32	26, Third posterolateral descending artery segment
33	27, Left posterolateral descending artery segment
34	28, Ramus intermedius segment
35	28a, Lateral ramus intermedius segment
36	29, Third diagonal branch segment
37	29a, Lateral third diagonal branch segment
97	Unknown

SAE Trigger (SAETrig) (form title/tab name)

Did the event meet a serious criterion(a)?	Did the event that met a serious criterion(a) also qualify as a protocol defined study efficacy endpoint of death, MI, stroke, or rehospitalization for recurrent UA?	Was event that met serious criterion(a) and qualified as a protocol defined study efficacy endpoint also assessed as being study drug related?

SAE Trigger reporting (section title)

1.	Did the event meet a serious criterion(a)? (R)	0 No 1 Yes
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2.	<p>Did the event that met a serious criterion(a) also qualify as a protocol defined study efficacy endpoint of death, MI, stroke, or rehospitalization for recurrent UA? NOTE: If the event is a hemorrhagic stroke, intracranial bleed or subdural hematoma with new neurological signs/symptoms consistent with a stroke, answer this question as "No". This event will be regarded as a study safety endpoint.</p> <p>(NR)</p>	<p>0 No</p> <p>1 Yes</p>
3.	<p>Was event that met serious criterion(a) and qualified as a protocol defined study efficacy endpoint also assessed as being study drug related? (NR)</p>	<p>0 No</p> <p>1 Yes</p>

Serious Adverse Event (SAE)
 (form title/tab name)

1	Date of birth	Report type	SAE occurred after initiation	Event Code	Event Term	Date event became serious	Date event resolved/stabilized/improved	Event Outcome	Serous Criteria	Relatedness to study drug	Relatedness to study procedure	Relevant Conditions not previously reported?	Action Taken with Study Drug	Date last taken	Reappear?	Clinically Significant Tests and Diagnostic Procedures					General narrative comments
																Laboratory Test/Procedure Name	Date and Time	Result	Units	Normal Limit	

Serious Adverse Event
 (section title)

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1.	Date of birth (R,SV)	/ / (1900 - 1993,DMY)
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Serious Adverse Event Reports
 (section title)

2.	Report type (R,SV)	<div>1 Initial report</div> <div>2 Follow-up report</div> <div>Follow-up report #</div> <div>Date of follow-up: / / (2008-2020,DMY)</div>
3.	Did SAE occur after initiation of study drug? (R,SV)	<div>1 Yes</div> <div>0 No</div>
4.	Event Code (R,SV)	E (N5)
5.	Event Term (diagnosis) (R,SV)	(A200)
6.	Date event became serious (R,SV)	/ / (2008-2020,UUU)
7.	Date event resolved/stabilized/improved (R,SV)	/ / (2008-2020,UUU)
8.	Event outcome (R,SV)	
9.	Serious criteria Check all serious criteria that apply (R, SV)	<div>1 Death</div> <div>2 Life-threatening at the time of the event</div> <div>4 Hospitalization <div>1 Required hospitalization <div>Hospitalization Tracking Number: H (N5)</div> <div>Date of admission: / / (2008-2020,UUU)</div> <div>Date of discharge: / / ((2008-2020,UUU)</div> </div> <div>2 Prolongation of existing hospitalization <div>Hospitalization Tracking Number: H (N5)</div> <div>Date of admission: / / (2008-2020,UUU)</div> <div>Date of discharge: / / ((2008-2020,UUU)</div> </div> </div>

3 Disability

1 Temporary

Start date: / / (2008-2020,UUU)

End date: / / (2008-2020,UUU)

2 Permanent

Start date: / / (2008-2020,UUU)

5 Congenital anomaly

8 Other

Provide details of any tests or procedures carried out to diagnose the SAE.					
	Laboratory Test/Procedure Name	Date and Time	Result	Units	Normal Limit
16.a					

Provide details of any tests or procedures carried out to diagnose the SAE.	
Lab Sequence Number <small>[hidden]</small>	<small>(A4)</small> <small>[calculated]</small>
Laboratory Test/Procedure <small>(R,SV)</small>	<small>(A200)</small>
Date and Time <small>(R,SV)</small>	<div> <div>/</div> <div>/</div> <div>:</div> <div><small>(2008-2020,UUUUUU)</small></div> </div>
Result <small>(R,SV)</small>	<small>(A50)</small>
Units <small>(NR, SV)</small>	<small>(A35)</small>
Normal Limit <small>(NR, SV)</small>	<div>Lower Limit of Normal <small>(N9.0)</small></div> <div>Upper Limit of Normal <small>(N9.0)</small></div>

<p>17. Provide a brief narrative description of SAE, possible other causes of the event (e.g. lack of efficacy, withdrawal of investigational product, the disease under study or other medical conditions) and details of the treatment. (NR,SV)</p>	<p>(A2000)</p>
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Pulldown List 1	
Value	Label
1	1
2	2
3	3
4	4
5	5
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8	8

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36	36
37	37
38	38
39	39
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49	49
50	50

Pulldown List 2	
Value	Label
1	Recovered
2	Recovering/Resolving
3	Not Recovered
4	Recovered with sequelae
5	Fatal
97	Unknown

End of Study (End of Study) *(form title/tab name)**(Page set up for PI signature)***End of Study** *(section title)*

1.	Did the subject complete the study? <i>(R)</i>	5 Screen failure 0 No 1 Yes
2.	Date of study termination/ last contact <i>(NR, SV)</i>	/ / <i>(2008-2020,DMY)</i>
3.	Type of Visit <i>(NR)</i>	4 Onsite visit 12 Telephone visit with the subject 3 No direct contact BUT other source of information used to define subject's vital status or if subject had an MI, stroke, stent thrombosis or bleeding (check all that apply): 60 Relative, First degree 35 Spouse 75 Neighbor 28 Friend 11 Health care provider 109 Public death registry 108 Hospital records 99 Other source of information 95 No direct contact and NO other source of information used to define subject's vital status or if subject had an MI, stroke, stent thrombosis or bleeding since the last visit

Study Completion Status [*hidden*]
(NR)

5 Screen failure
N No
Y Yes

Reason for Termination *(section title)*

4.	Reason for ending participation in the study (NR, SV)	<p>1 Completed</p> <p>3 Death</p> <p>5 Screen failure (<i>mapped</i>)</p> <p>27 Subject decision; withdrawal from participation in study. (REVERSED ORDER)</p> <p>28 Subject decision; revocation of consent.</p> <p>4 Impossible to locate and establish contact with the subject. Please explain attempts to contact:</p> <p style="text-align: right;">(A200)</p> <p>9 Sponsor decision</p> <p>8 Physician decision</p>
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Vital Status (Vital Status) *(form title/tab name)***Vital Status** *(section title)*

1.	Date that vital status was obtained (R)	/ / (2008-2020,DMY)
2.	Vital Status (R,SV)	<div>1 Subject known to be alive at study closure</div> <div>2 Subject known to be dead at study closure (please complete death endpoint form)</div> <div>4 Not known if the subject is alive at study closure. Date last known to be alive:</div> <div>/ / (2008-2020,DMY)</div>

PCAE/Procedure/Medication Summary (SUMMARY) *(form title/tab name)*
Adverse Events, Medications and Procedures Since the Last Visit *(section title)*

1.	Has there been a PCI since the last study visit? <i>(R)</i>	0 No 1 Yes 97 Unknown
2.	Has there been an interruption or discontinuation of study drug since the last study visit? <i>(R)</i>	0 No 1 Yes 97 Unknown
3.	Have there been any transfusions since the last study visit? <i>(R)</i>	0 No 1 Yes 97 Unknown
4.	Has there been a diagnostic catheterization since the last study visit? <i>(R)</i>	0 No 1 Yes 97 Unknown
5.	Has there been a CABG performed since the last study visit? <i>(R)</i>	0 No 1 Yes 97 Unknown
6.	Has the subject started aspirin therapy since the last visit <i>OR</i> has there been a change in the dosage of aspirin prescribed since the last study visit? <i>(R)</i>	0 No 1 Yes 97 Unknown

7.	Has there been a new medication prescribed since the last visit, <i>OR</i> has an existing medication been stopped since the last study visit? <i>(R)</i>	0 No 1 Yes 97 Unknown
8.	Has there been a change to a pre-existing condition or previously reported adverse event since the last visit <i>OR</i> has there been a new adverse event since the last study visit? <i>(R)</i>	0 No 1 Yes 97 Unknown
9.	Has there been a hospitalization, outpatient visit or emergency department visit since the last study visit? <i>(R)</i>	0 No 1 Yes 97 Unknown
10.	Has the subject or the subject's spouse become pregnant or began breast feeding since the last study visit? <i>(R)</i>	0 No 1 Yes 97 Unknown
	Pregnancy [<i>hidden</i>] <i>(NR)</i>	<i>(N1.0)</i>

Verify Now Platelet Function Measurements (PFMU) *(form title/tab name)***Verify Now Platelet Function Measurements** *(section title)*

Please note: The results from the Verify Now device are encrypted.	
1. Adverse Event code (R,SV)	E (N5)
2. P2Y ₁₂ assay: (R, SV)	90 / / : (2008-2020,DMYHM) Result (encrypted): PRU (A9) % Inhibition (A9) Base (A9) 93 Not done Error/attention message received
3. Date and time of specimen collection: (R, SV)	90 / / : (2008-2020,DMYHM) 93 Not done

Last study drug maintenance dose reporting *(section title)*

4. Date and time of most recent study drug maintenance dose? (R,SV)	/ / : (2008-2020,DMYHM)
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Percutaneous Coronary Interventional Procedure (PCI) (form title/tab name)

Date PCI performed	Hospital Tracking Number	Circumstance	Access site	Date and time sheath inserted	Date and time sheath removed	Access site closure method	Did the intervention result in Procedural Complications ?	Did the intervention result in a subsequent surgical procedure?	Did the subject receive anticoagulants for this procedure?	Did the subject receive a GP IIb/IIIa inhibitor for this procedure?	Were any cardiac biomarkers elevated greater than 3 times the upper limit of normal within 24 hours following the procedure?	Did a hematoma occur at the access site?	Numbe of lesions treated
1.													
2.													
3.													

Percutaneous Coronary Interventional Procedure Entry (section title)

1.	Date PCI performed (R, SV)	/ / (2008-2020,DMY)
	PCI number [CALCULATED] (NR)	(N10)
2.	Hospital Tracking Number (R)	90 H (N5) 96 Not applicable
3.	Circumstance (R)	2 Elective 6 Urgent/Emergent
4.	Access site (R)	1 Check all that apply: 19 Femoral artery 487 Femoral vein 21 Radial artery 14 Brachial artery 99 Other 97 Unknown
5.	Date and time sheath inserted (R)	/ / : (2008-2020,DMYUU)
6.	Date and time sheath removed (R)	/ / : (2008-2020,DMYUU)
7.	Access site closure method (R)	89 Mechanical pressure device 90 Closure device 88 Manual pressure 97 Unknown
8.	Did the intervention result in Procedural Complications? (R)	1 If Yes, check all that apply: 2334 Coronary perforation 2335 Cardiac rupture 2331 Pericardial tamponade 99 Other complications 97 Unknown 95 No complications
9.	Did the intervention result in a subsequent surgical procedure? (R)	1 If Yes, check all that apply: 179 Urgent coronary artery bypass graft surgery 331 Urgent peripheral vascular surgery 99 Other surgical procedures 97 Unknown 95 No surgical procedures
10.	Did the subject receive anticoagulants for this procedure? (R)	0 No 1 Yes 97 Unknown
11.	Did the subject receive a GP IIb/IIIa inhibitor for this procedure? (R)	0 No 1 Yes 97 Unknown
12.	Were any cardiac biomarkers elevated greater than 3 times the upper limit of normal within 24 hours following the procedure? (R)	0 No 1 Yes 97 Unknown

Percutaneous Coronary Interventional Diagnosis Entry (section title)

13.	Did a hematoma occur at the access site? (R)	96 No 216 Yes, provide date and time that hematoma was first noted: / / : (2008-2020,UUYUU) 97 Unknown
14.	Number of lesions treated (R)	(N3)

PCI lesion(s)/vessel(s) (section title)

Note: Use Add Entry to record EACH lesion associated with a PCI.

Lesion number	Site of coronary lesion	Vessel type	Location of lesion in graft (if vein graft or arterial graft is checked above)	Lesion type	Lesion risk	Lesion length	Bifurcation lesion	Peri-procedural angiographic findings?	Outcome	Was IVUS guidance used?	Intracoronary device(s)	How many stents were implanted?
15.a												

Lesion number [CALCULATED using the PCI number as the first digits] (NR)	(N10)
Site of coronary lesion (R, SV)	
Vessel type (R, SV)	490 Native coronary artery 489 Saphenous vein bypass graft 13 Arterial bypass graft
Location of lesion in graft (if vein graft or arterial graft is checked above) (NR)	493 Body of graft 494 Aortic anastomosis 452 Distal anastomosis
Lesion type (R)	28 De Novo 31 Restenosis
Lesion risk (R)	63 Non-High risk (Non C) 64 High risk (C)
Lesion length (R)	mm (N11.1)
Bifurcation lesion (R)	0 No 1 Yes
Peri-procedural angiographic findings? (R)	1 No reflow phenomenon 2 New thrombus 5 Dissection 4 Acute Closure 3 Side Branch closure 6 Distal embolization 95 None of the above
Outcome (R)	6 Successful (Reduction of stenosis to less than 20% and TIMI 3 flow) 7 Not successful
Was IVUS guidance used? (R)	0 No 1 Yes
Intracoronary device(s) (R)	87 Stent 74 Balloon 93 Distal protection device 94 Thrombectomy device 95 Atherectomy device 99 Other
How many stents were implanted?	1 Number of stents 96 Not applicable

Stent information (section title)

Note: Use Add Entry to record EACH stent associated with a lesion.

	Lesion number	Stent number	Diameter of vessel stented	Type of stent implanted	Stent length	Stent diameter	Maximum post stent balloon inflation pressure	Diameter of balloon	Length of balloon	IVUS guidance used?	Was this stent overlapped with another stent?
16.a											

Stent information Entry (section title)

Lesion number (R)	(N10)
Stent number [CALCULATED using the Lesion number as the first digits] (NR)	(N10)
Diameter of vessel stented (R)	mm (N11.1)
Type of stent implanted (R, SV)	79 Drug eluting stent (DES) 77 Bare Metal stent (BMS) 99 Other
Stent length (R)	mm (N11.1)
Stent diameter (R)	mm (N11.1)

Maximum post stent balloon inflation pressure (R)	97 Unknown atmospheres <i>N(1.1)</i> 96 Not applicable
Diameter of balloon used for post stent dilatation (R)	97 Unknown 1 mm <i>(N(1.1))</i> 96 Not applicable
Length of balloon used for post stent dilatation (R)	97 Unknown 1 mm <i>(N(1.1))</i> 96 Not applicable
IVUS guidance used? (R)	0 No 1 Yes
Was this stent overlapped with another stent? (R)	0 No 1 Yes 97 Unknown 96 Not applicable

Pulldown List 1	
Value	Label
1	1, Proximal right coronary artery conduit segment
2	2, Mid-right coronary artery conduit segment
3	3, Distal right coronary artery conduit segment
4	4, Right posterior descending artery segment
5	5, Right posterior atrioventricular segment
6	6, First right posterolateral segment
7	7, Second right posterolateral segment
8	8, Third right posterolateral segment
9	9, Posterior descending septal perforators segment
10	10, Acute marginal segment (s)
11	11, Left main coronary artery segment
12	12, Proximal LAD artery segment
13	13, Mid-LAD artery segment
14	14, Distal LAD artery segment
15	15, First diagonal branch segment
16	15a, Lateral first diagonal branch segment
17	16, Second diagonal branch segment
18	16a, Lateral second diagonal branch segment
19	17, LAD septal perforators segment
20	18, Proximal circumflex artery segment
21	19, Mid-circumflex artery segment
22	19a, Distal circumflex artery segment
23	20, First obtuse marginal branch segment
24	20a, Lateral first obtuse marginal branch segment
25	21, Second obtuse marginal branch segment
26	21a, Lateral second obtuse marginal branch segment
27	22, Third obtuse marginal branch segment
28	22a, Lateral third obtuse marginal branch segment
29	23, Circumflex artery AV groove continuation segment
30	24, First left posterolateral branch segment
31	25, Second left posterolateral branch segment
32	26, Third posterolateral descending artery segment
33	27, Left posterolateral descending artery segment
34	28, Ramus intermedius segment
35	28a, Lateral ramus intermedius segment
36	29, Third diagonal branch segment
37	29a, Lateral third diagonal branch segment
97	Unknown

Baseline/Visit 1 Malignancy History (form title/tab name)

Malignancy History Entry (section title)

1.	Is there a family history of colon cancer (first degree relative)? (R, SV)	1 Yes 0 No 97 Unknown
2.	Is there a family history of breast cancer (first degree relative)? (R, SV)	1 Yes 0 No 97 Unknown
3.	Is there a personal history of any malignancies? (R), SV)	1 Yes 0 No 97 Unknown
4.	As the result of the physical exam for this visit, were there any signs or symptoms suggestive of a possible malignancy that has not yet been diagnosed? (R,SV)	216 Yes (check all that apply) 1 Blood in stool 2 Blood in urine (hematuria) 3 Vaginal bleeding 4 Coughing up blood (hemoptysis) 5 Breast mass 99 Other, Specify (A200) 96 No 97 Unknown
5.	Has the subject had any cancer screening tests/ exams prior to randomization? (R, SV)	0 No 1 Yes 97 Unknown

Screen/Test Exam (section title)

Type of screening test/exam	Date of screening test/exam (most recent)	Was the result of the most recent screening test/exam suggestive of a possible malignancy?
-----------------------------	---	--

6a.	Type of screening test/exam (NR, SV)	482 Colonoscopy 125 Computed Tomography (CT), Specify <div>(A200)</div> 550 Fecal immunochemical test 551 Fecal occult blood 141 Mammography 140 Magnetic Resonance Imaging (MRI), Specify <div>(A200)</div> 147 Pap Smear 552 Prostate Specific Antigen (PSA) 537 Sigmoidoscopy 553 Stool DNA test 164 Ultrasound, Specify <div>(A200)</div> 99 Other, Specify <div>(A200)</div>
6b.	Date of screening test/exam (most recent) (NR, SV)	/ / (1908-2020,UUY)
6c.	Was the result of the most recent screening test/exam suggestive of a possible malignancy? (NR, SV)	0 No 1 Yes 97 Unknown

Alcohol Use (section title)

7.	Does the subject consume alcohol?(R, SV)	1 Yes Daily Regularly (specifies a subject engages frequently in the habit in question but not to the degree of daily use) Irregularly (indicates a subject continues to engage in the habit more than occasionally but not in accordance with a customary pattern) Occasionally (specifies a subject seldom engages in the habit in question, only on special occasions such as a holiday) 97 Unknown 0 No
----	--	---

8.	Is the subject postmenopausal? (R, SV)	<div>1 Yes, Onset Year</div> <div>(1900-2020, YYYY)</div> <div>0 No</div> <div>97 Unknown</div> <div>96 Not applicable</div>
9.	Has the subject used hormonal replacement therapy? (NR, SV)	<div>1 Yes</div> <div>Past</div> <div>Number of years (N3)</div> <div>Stop date / (1900-2020, UY)</div> <div>Current</div> <div>0 No</div> <div>97 Unknown</div>

Post Baseline Malignancies *(form title/tab name)*
Malignancy Entry *(section title)*

1.	Has the subject been newly diagnosed with a malignancy since the last visit? <i>(R, SV)</i>	1 Yes 0 No 97 Unknown
2.	As the result of the physical exam for this visit, were there any signs or symptoms suggestive of a possible malignancy that has not yet been diagnosed? <i>(R, SV)</i>	216 Yes (check all that apply) 1 Blood in stool 2 Blood in urine (hematuria) 3 Vaginal bleeding 4 Coughing up blood (hemoptysis) 5 Breast mass 99 Other, Specify (A200) 96 No 97 Unknown
3.	Has the subject had any cancer screening tests/exams since the last visit? <i>(R, SV)</i>	0 No 1 Yes 97 Unknown

Screening/Test Exam *(section title)*

Type of screening test/exam	Date of screening test/exam (most recent)	Was the result of the most recent screening test/exam suggestive of a possible malignancy?
-----------------------------	---	--

4a.	Type of screening test/exam <i>(NR, SV)</i>	482 Colonoscopy 125 Computed Tomography (CT). Please specify. (A200) 550 Fecal immunochemical test 551 Fecal occult blood 141 Mammography 140 Magnetic Resonance Imaging (MRI). Please specify. (A200) 147 Pap Smear 552 Prostate Specific Antigen (PSA) 537 Sigmoidoscopy 553 Stool DNA test 164 Ultrasound. Please specify. (A200)
-----	---	---

		99 Other. Please specify.	(A200)
4b.	Date of screening test/exam (most recent) (NR, SV)	/ / (2008-2020, DMY)	
4c.	Was the result of the most recent screening test/exam suggestive of a possible malignancy? (NR, SV)	0 No 1 Yes 97 Unknown	

Malignancy PCAE Pre- or Post-Randomization (*form title/tab name*)**Malignancy PCAE Entry** (*section title*)**Complete items 1-14 for the initial entry of this event**

1.	Onset visit number (R, SV)	
2.	Event Term (R, SV)	(A200)
	Event code (R)	E (N5) [Calculated - starting with number 500]
3.	Date of initial detection of malignancy (R, SV)	1 / / (1908-2020,UUY) 97 Unknown
4.	Date of histologic diagnosis (R, SV)	1 / / (1908-2020,UUY) 97 Unknown
5.	Location of primary malignancy (R, SV)	1 20 Skin. Please specify. (A200) 99 Other, specify (A200)
6.	Stage of malignancy at diagnosis (R, SV)	1 96 Not applicable. Please provide a comment. (A200) 97 Unknown. Please provide a comment. (A200)

7.	If staging was incomplete or unknown, select one of the following: (NR, SV)	<div>19 Local disease</div> <div>18 Regional disease</div> <div>17 Metastatic disease</div> <div>96 Not applicable. Please provide a comment.</div> <div>(A200)</div> <div>97 Unknown. Please provide a comment.</div> <div>(A200)</div>
8.	Is the cancer metastatic? (R, SV)	<div>0 No</div> <div>1 Yes</div> <div>97 Unknown</div>
9.	Status at time of initial entry of event (R, SV)	
10.	Has there ever been any treatment of this malignancy? (R, SV)	<div>1 Yes</div> <div>0 No treatment</div> <div>97 Unknown</div>
11.	Did the malignancy meet a 'serious' criteria during this visit interval? (R, SV)	<div>0 No</div> <div>1 Yes, check all that apply</div> <div>1 Death</div> <div>2 Life-threatening at the time of the event</div> <div>3 Disability</div> <div>4 Hospitalization (does not include hospitalization for a planned treatment of the malignancy)</div> <div>5 Congenital anomaly</div> <div>8 Other</div> <div>97 Unknown</div>

12.	Narrative (R, SV)	<div>(A2000)</div>
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Malignancy Entry (section title)

13.	Record the last or most recent date of treatment since diagnosis (NR, SV)	<div><div>2</div><div>Radiation</div><div>/ / (1908-2020,UUY)</div><div>1</div><div>Chemotherapy</div><div>/ / (1908-2020,UUY)</div><div>4</div><div>Hormonal</div><div>/ / (1908-2020,UUY)</div><div>6</div><div>Surgical</div><div>/ / (1908-2020,UUY)</div><div>3</div><div>Immunotherapy</div><div>/ / (1908-2020,UUY)</div><div>8</div><div>Other treatment</div><div>/ / (1908-2020,UUY)</div><div>(A200)</div></div>
-----	---	---

14.	Which of these items prompted the evaluation that led to the diagnosis of the malignancy? <i>(R, SV)</i>	<div>1</div> <div>3 Bleeding, specify location (A200)</div> <div>99 Other, specify (A200)</div>
	CEC Tracking Number <i>(NR)</i> <i>(calculated)</i>	<div>(read only)</div>

This section should be completed at every six-month interval visit.

Additional Information *(section title)*

	Interval CEC Tracking Number	Visit Number	Status at this visit	Is the cancer metastatic	Current treatment of the malignancy at this visit	Did the malignancy meet a 'serious' criteria during this visit interval?
15a.						
15b.						
15c.						

	Interval CEC Tracking Number <i>(calculated CEC Tracking Number + 1 for each interval))</i>	<div>(read only)</div>
15a.	Visit Number <i>(R, SV)</i>	
15b.	Status at this visit <i>(R, SV)</i>	
15c.	Is the cancer metastatic? <i>(R, SV)</i>	<div>0 No</div> <div>1 Yes</div> <div>97 Unknown</div>

15d.	Current treatment of the malignancy at this visit (R, SV)	<div> 1 Check all that apply <div> 2 Radiation 1 Chemotherapy 4 Hormonal 6 Surgical 3 Immunotherapy 8 Other treatment (Specify) </div> </div> <div>(A200)</div> <div>0 No treatment</div>
15e.	Did the malignancy meet a 'serious' criteria during this visit interval? (R, SV)	<div>0 No</div> <div>1 Yes, check all that apply</div> <div> 1 Death 2 Life-threatening at the time of the event 3 Disability 4 Hospitalization (does not include hospitalization for a planned treatment of the malignancy) 5 Congenital anomaly 8 Other </div> <div>97 Unknown</div>

Pulldown List 1

Value	Label
1	Visit 1
2	Visit 2
3	Visit 3
4	Visit 4
5	Visit 5
6	Visit 6
7	Visit 7
8	Visit 8
9	Visit 9
10	Visit 10
11	Visit 11
12	Visit 12
14	Early Discontinuation of Study Drug
15	Final Visit

Pulldown List 2	
Value	Label
1	Blood
2	Bone
3	Bone marrow
4	Brain
5	Breast
6	Cervix
7	Colorectal
8	Esophagus
9	Eye
10	Gallbladder
11	Kidney
12	Liver
13	Lung/bronchus
14	Lymphatics
15	Oral cavity
16	Ovary
17	Pancreas
18	Pharynx
19	Prostate
21	Stomach
22	Urethral
23	Urinary bladder
24	Uterus
26	Unknown primary

Pulldown List 3

<u>Value</u>	<u>Label</u>
1	Stage 0 (cancer in situ)
2	Stage I
3	Stage II
4	Stage III
5	Stage IV
6	Staging incomplete

Pulldown List 4

<u>Value</u>	<u>Label</u>
0	No evidence of disease
1	Active disease
2	Stable/Inactive disease
96	Not applicable

Pulldown List 5

<u>Value</u>	<u>Label</u>
0	Asymptomatic routine cancer screening
1	Routine physical exam
2	Anemia

Malignancy PCAE Adjudication *(form title/tab name)*

1.	Was this a CEC-triggered event? <i>(NR)</i>	0 No 1 Yes
----	---	---------------

Malignancy Adjudication Entry *(section title)*

	Interval CEC Tracking Number	Has a malignancy been confirmed	Status of neoplasm	Date of initial detection of the malignancy	Date of histological diagnosis	Location of primary malignancy	Stage of malignancy at diagnosis	If staging was incomplete or unknown, select one of the following:	Is the confirmed malignancy a recurrence of a cancer that was present prior to randomization	Select the method(s) by which the malignancy was initially detected.	Interval CEC Tracking Status	Date of adjudication
2a.												
2b.												
2c.												

2a.	CEC Tracking Number <i>(R)</i>	(A19)
2b.	Has a malignancy been confirmed? <i>(R)</i>	1 Yes 0 No 94 Cannot be determined
2c.	Status of neoplasm <i>(NR)</i>	
2d.	Date of initial detection of the malignancy <i>(NR)</i>	/ / (1908-2012,UUY)

2e.	Date of histological diagnosis <i>(NR)</i>	/ / (1908-2012,UUY)
2f.	Location of primary malignancy <i>(NR)</i>	<p>1 If Other. Please specify. (A200)</p> <p>271 Skin</p> <p>1 Basal cell</p> <p>2 Squamous cell</p> <p>3 Melanoma</p> <p>99 Other, specify (A200)</p>
2g.	SEER Classification of primary malignancy <i>(NR)</i>	
2h.	Stage of malignancy at diagnosis <i>(NR)</i>	
2i.	If staging was incomplete or unknown, select one of the following: <i>(NR)</i>	<p>19 Local disease</p> <p>18 Regional disease</p> <p>17 Metastatic disease</p> <p>96 Not applicable. Please provide a comment. (A200)</p> <p>97 Unknown. Please provide a comment. (A200)</p>
2j.	Did the patient have a known history of this Malignancy? <i>(NR)</i>	<p>1 Yes</p> <p>If yes, what is this malignancy? (check only one)</p> <p>1 Recurrence</p> <p>2 Progression</p> <p>3 New Primary</p> <p>97 Unknown</p> <p>0 No</p> <p>94 Cannot be determined</p>
2k.	Grading of malignancy (check only one) <i>(NR)</i>	

2l.	Select the method(s) by which the malignancy was initially detected. (check all that apply) (NR)	<p>1 Asymptomatic routine cancer screening (check all that apply)</p> <p>482 Colonoscopy</p> <p>125 Computed Tomography (CT). Please specify.</p> <p>(A200)</p> <p>550 Fecal immunochemical test</p> <p>551 Fecal occult blood</p> <p>141 Mammography</p> <p>140 Magnetic Resonance Imaging (MRI). Please specify.</p> <p>(A200)</p> <p>147 Pap Smear</p> <p>552 Prostate Specific Antigen (PSA)</p> <p>154 Physical Exam</p> <p>537 Sigmoidoscopy</p> <p>553 Stool DNA test</p> <p>164 Ultrasound. Please specify.</p> <p>(A200)</p> <p>99 Other. Please specify.</p> <p>(A200)</p> <p>2 Symptomatic cancer screening (check all that apply)</p> <p>482 Colonoscopy</p> <p>125 Computed Tomography (CT). Please specify.</p> <p>(A200)</p> <p>550 Fecal immunochemical test</p> <p>551 Fecal occult blood</p> <p>141 Mammography</p> <p>140 Magnetic Resonance Imaging (MRI). Please specify.</p> <p>(A200)</p> <p>147 Pap Smear</p> <p>552 Prostate Specific Antigen (PSA)</p> <p>154 Physical Exam</p> <p>537 Sigmoidoscopy</p> <p>553 Stool DNA test</p>
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		<p>164 Ultrasound. Please specify.</p> <p style="text-align: right;">(A200)</p> <p>99 Other. Please specify.</p> <p style="text-align: right;">(A200)</p> <p>3 Evaluation of anemia</p> <p>4 Evaluation of a bleeding event (check all that apply)</p> <p> 44 Breast</p> <p> 208 Epistaxis</p> <p> 448 Gastrointestinal</p> <p> 347 Hematuria</p> <p> 255 Hemoptysis</p> <p> 349 Vaginal</p> <p> 99 Other. Please specify.</p> <p style="text-align: right;">(A200)</p> <p>5 Diagnostic procedures done for a suspected cancer not associated with a bleeding event or anemia</p> <p> 253 Biopsy</p> <p> 554 Imaging</p> <p> 210 Laboratory</p> <p> 99 Other. Please specify.</p> <p style="text-align: right;">(A200)</p> <p>6 Diagnostic procedures done for a reason/symptom not related to a suspected cancer, bleeding event, or anemia</p> <p> 253 Biopsy</p> <p> 554 Imaging</p> <p> 210 Laboratory</p> <p> 99 Other. Please specify.</p> <p style="text-align: right;">(A200)</p>
2m.	CEC Tracking Status (R)	
2n.	Date of adjudication (R)	/ / (2010-2012,DMY)

Final Malignancy Adjudication Entry (section title)

3.	CEC Tracking Number <i>(NR)</i>	(A19)
4.	CEC Tracking Status <i>(NR)</i>	
5.	Date of final assessment of malignancy <i>(NR)</i>	/ / (2010-2012,DMY)
6.	Final malignancy status <i>(NR)</i>	
7.	Did the subject die due to this malignancy? <i>(NR)</i>	<div>1 Yes</div> <div>0 No</div> <div>96 Not applicable</div> <div>94 Cannot be determined</div>

Pulldown List 1	
Value	Label
1	Blood
2	Bone
3	Bone marrow
4	Brain
5	Breast
6	Cervix
7	Colorectal
8	Esophagus
9	Eye
10	Gallbladder
11	Kidney
12	Liver
13	Lung/bronchus
14	Lymphatics
15	Oral cavity

99	Other
16	Ovary
17	Pancreas
18	Pharynx
19	Prostate
21	Stomach
22	Urethral
23	Urinary bladder
24	Uterus
26	Unknown primary

Pulldown List 2

<u>Value</u>	<u>Label</u>
1	Stage 0 (cancer in situ)
2	Stage I
3	Stage II
4	Stage III
5	Stage IV
6	Staging incomplete
97	Unknown

Pulldown List 3

<u>Value</u>	<u>Label</u>
1	New
2	Outstanding source documents
3	Phase I Review
4	Committee Review (Phase II)

5	Resolved/completed
6	No action needed
7	Hold
8	Re-review

Pulldown List 4	
Value	Label
15	Anus
2	Bone and joint
3	Brain and other nervous system
58	Breast
18	Cervix uteri
12	Colon and rectum
19	Corpus and uterus, NOS
9	Esophagus
16	Eye and orbit
27	Kidney and renal pelvis
28	Larynx
31	Acute lymphocytic leukemia
32	Chronic lymphocytic leukemia
34	Acute myeloid leukemia
36	Chronic myeloid leukemia
29	Leukemia
37	Liver and intrahepatic bile duct
38	Lung and bronchus
59	Lymphoma

39	Melanoma of skin
44	Myeloma
45	Oral cavity and pharynx
60	Other endocrine
24	Hodgkin Lymphoma
25	Non-Hodgkin Lymphoma
61	B-cell Non-Hodgkin Lymphoma
62	T-cell Non-Hodgkin Lymphoma
20	Ovary
52	Pancreas
53	Prostate
63	Other Non-epithelial skin
64	Skin
11	Small intestine
54	Soft tissue including heart
10	Stomach
55	Testis
56	Thyroid
47	Tongue
57	Urinary bladder
22	Vulva
94	Cannot be determined

Pulldown List 5	
Value	Label

1	Low
2	Intermediate
3	High
94	Cannot be determined
97	Unknown

Pulldown List 6	
<u>Value</u>	<u>Label</u>
35	No evidence of disease
36	Active disease
6	Stable/Inactive disease
94	Cannot be determined
96	Not applicable

Leo Document ID = 0836cb58-6707-4143-a53a-a5185088c2fa

Approver: Kenneth J Winters (AM\RM93288)
Approval Date & Time: 04-May-2012 20:33:38 GMT
Signature meaning: Approved

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Approval Date & Time: 07-May-2012 16:02:17 GMT
Signature meaning: Approved

Confidential Information

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**Clinical Endpoint Committee Charter
for Cancer Adjudication for Protocol H7T-MC-TABY (b):
A Comparison of Prasugrel and Clopidogrel in Acute
Coronary Syndrome (ACS) Subjects with Unstable
Angina/Non-ST-Elevation Myocardial Infarction
(UA/NSTEMI) Who are Medically Managed – The
TRILOGY ACS Study
Prasugrel (LY640315)**

CEC Charter Approved:
October 27, 2010

Table of Contents

Section	Page
Abbreviations	4
Overview of Revisions.....	6
1. Introduction.....	11
2. Role of the DCRI CEC	12
3. CEC Committee Organizations.....	13
3.1 Selection of CEC Members	13
3.2. Qualifications of the CEC Physician Reviewers	14
3.3. Clinical Events Classification Personnel	14
3.3.1. CEC Director	14
3.3.2. DCRI CEC-CA Chairperson.....	14
3.3.3. DCRI CEC-CA Coordinator	14
3.3.4. CEC-CA Physicians.....	15
3.3.5. Clinical Data Assistants	15
3.3.6. Support Staff	16
3.4. Contract Research Organization (CRO)	16
3.5. Study Operations Committee.....	17
4. Operations	17
4.1. CEC Meetings.....	17
4.2. Identification of Suspected Events.....	17
4.3. Collection of Data	18
4.4. Cancer Definitions	18
4.5. CEC-CA.....	20
4.6. Quality Control (QC)	20
5. Confidentiality	21
6. CEC-CA Process Flow	22
7. Documentation.....	23

Appendix A: Source Documents Needed for Events.....	24
Appendix B: CEC-CA Critical Variable Data	25
Appendix C: List of CEC-CA Personnel	26
Appendix D: CEC Committee Members	27
8. References.....	29

Abbreviations

Abbreviation/Acronym	Definition
ACC	American College of Cardiology
ACS	Acute Coronary Syndrome
ARO	Academic Research Organization
CABG	coronary artery bypass graft
CEC	Clinical Endpoints Committee/Clinical Events Classification
CECPI	Appropriate faculty level physician serving as CEC Primary Investigator
CK-MB	creatinine kinase- Muscle Brain (fraction primarily in cardiac muscle)
CRF	case report form
CRO	contract research organization
CT	computerized tomography
CV	cardiovascular
DMC	Data Monitoring Committee
DCRI	Duke Clinical Research Institute
ECG	electrocardiogram
eCRF	Electronic case report form
FDA	Food and Drug Administration
FFP	fresh frozen plasma
Hct	hematocrit
Hgb	hemoglobin
ICH	intracranial hemorrhage
InForm™	Commercial software for electronic data capture
MI	myocardial infarction
MRI	magnetic resonance image
NSTEMI	Non-ST segment elevation myocardial infarction
PCI	percutaneous coronary intervention
PRBC	packed red blood cells
PT	preferred term
QC	Quality Control
STEMI	ST segment elevation myocardial infarction
TIA	transient ischemic attack

TIMI	The TIMI Study Group. Named for a series of national clinical studies known as the TIMI (Thrombolysis in Myocardial Infarction) studies launched in 1984 by Brigham and Women's Hospital.
UA	unstable angina
ULN	upper limit of normal

Overview of Revisions

Revisions from TRILOGY ACS Neoplasm Charter Version 1.0 July 15, 2009 to V2

Version V1: Section 1.0

Though, like TRITON, TRILOGY ACS is not designed to rigorously answer questions about cancer, and even the most thorough data collection and analysis will have limitations.

Version 2: Section 1.0

Because, like TRITON, TRILOGY ACS is not designed to rigorously answer questions about cancer, and even the most thorough data collection and analysis will have limitations.

Version V1: Section 2.0

The items that the CEC-CA will evaluate at study-end are:

- date of final assessment for neoplasm
- status of disease

Version 2: Section 2.0

The items that the CEC-CA will evaluate at study conclusion or at the time of death (for patients who die before study conclusion) for patients who have a positively adjudicated new or recurrent malignancy are:

Date of final assessment for neoplasm

- status of disease at final assessment (or at time of death, when appropriate)
- status of disease at final assessment (or at time of death, when appropriate)

Version 1: Section 2.0

The CEC-CA will confirm the occurrence and the onset date of each suspected cancer based on the preponderance of evidence and clinical judgment of the expert physician reviewers. If there is a discrepancy between the CEC-CA adjudication result and the site-reported data, including date of event onset, the CEC adjudication result will override the site reported data and will be used in the final statistical analysis.

The adjudicated results will be electronically entered into the clinical database by the CEC through InForm™ on an ongoing basis. Adjudication reports in InForm™ will be reviewed by the CRO safety group in real time.

Version 2: Section 2.0

The cause of death adjudication results from the CEC-CA will be separately adjudicated and recorded compared with the cause of death adjudication results from the main CEC (where cardiovascular death is a component of the composite primary endpoint of the study). The CEC-CA will only adjudicate whether deaths were malignancy-related or not malignancy-related and will only evaluate deaths for patients who had a preceding positively adjudicated new or recurrent malignancy. It is expected that there will be disagreement between the main CEC death adjudication results and the CEC-CA death adjudication results for the applicable patients. No attempts will be made to resolve these disagreements for the purposes of the main study efficacy results. The CEC-CA death adjudication results will be utilized only for analyses, presentations, and publications relating to the cancer adjudication activities within this study whereas the main CEC death adjudication results will be utilized for all other analyses, presentations, and publications related to the main study results. In particular, the primary endpoint analyses of the TRILOGY – ACS study will be performed solely using the main CEC adjudication results. The analyses, presentations, and publications relating to the cancer adjudication activities will list and compile the disagreements relating to the death adjudication results between the main CEC and CEC-CA

Version 1.0 Section 3.2

Qualifications of the CEC-CA Physician Reviewers

CEC-CA physician reviewers will have the following: a current license to practice medicine; current clinical experience in general oncology (with one member with experience in gastrointestinal cancer); expertise in the diagnosis, staging and management of cancers; board certification or board eligibility; and relevant clinical trial experience. Documentation of the required qualifications is maintained at the DCRI in the form of current curriculum vitae for the CEC-CA selected member.

Version 2.0 Section 3.2

Qualifications of the CEC-CA Physician Reviewers

Oncology: CEC-CA physician reviewers will have the following: a current license to practice medicine; current clinical experience in general oncology (with one member with experience in gastrointestinal cancer); expertise in the diagnosis, staging and management of cancers; board certification or board eligibility; and relevant clinical trial experience.

The CEC-CA will also have a member who is a Gastroenterologist that has a current license to practice medicine; current clinical experience experienced in gastrointestinal related cancers; board certification or board eligibility; and relevant clinical trial experience.

Documentation of the required qualifications is maintained at the DCRI in the form of current curriculum vitae for the CEC-CA selected member.

Version 1.0: Section 3.4

CEVA will be the primary contact responsible for managing the North American sites and the primary contact responsible for managing the International sites to facilitate the resolution of outstanding CEC-CA eCRF and/or source document queries.

Version 2.0: Section 3.4

CEVA will be the primary contact responsible for managing sites to facilitate the resolution of outstanding CEC-CA eCRF and/or source document queries.

Version 1.0: Section 4.2

The program will compare preferred terms that are specified by physician reviewers from DCRI, Daiichi Sankyo and Eli Lilly to investigator reported endpoints. The unreported events will be referenced as CEC-identified suspected cancer events and will be adjudicated by the CEC-CA for review.

Version 2.0: Section 4.2

The program will compare preferred terms that are specified by physician reviewers from DCRI, Daiichi Sankyo and Eli Lilly to investigator reported endpoints. The sites will be asked to enter these events into the eCRF. If a site declines this request than the unreported events will be referenced as CEC-identified suspected cancer events and will be adjudicated by the CEC-CA for review.

Version 1.0: Section 4.4

Date of Initial Detections: This will be the date that the patient demonstrated either clinical or radiological (imaging) evidence of cancer.

Version 2.0: Section 4.4

Date of Initial Detections: This will be the date that the patient demonstrated either clinical symptoms consistent with cancer in the opinion of the treating physician or where there is radiological (imaging) or procedural evidence of cancer detected through diagnostic procedure(s). Whichever date can be confirmed to occur first will be used.

Version 1.0: Section 4.5

All suspected cancer events that are considered as “active” at randomization or detected after randomization will be adjudicated collectively by the CEC-CA committee. Cancers that are identified by the sites as “Stable/Inactive” at randomization will not be adjudicated by the CEC-CA committee. A CEC-CA committee will consist of at least three CEC-CA physicians at each committee meeting.

The CEC-CA will not adjudicate cause of death for cases where it is suspected that a cancer event contributed to the cause of death. Cause of death will be adjudicated by the CEC for TRILOGY ACS.

Version 2.0: Section 4.5

The CEC-CA will adjudicate cause of death (malignancy-related or not) in all subjects with malignancy at any point in the study, independent of the primary CEC. However, the primary endpoint and all other pre-defined analyses involving attributed death would employ the primary CEC adjudication.

Revisions from TRILOGY ACS Neoplasm Charter Version 2.0 to V3.0

Version 3.0: Overview of Revisions

Addition of: Revisions from TRILOGY ACS Neoplasm Charter Version 1.0 July 15, 2009 to V2

Version 2.0: Appendix B

Initial Diagnosis

Form 530: Baseline /Visit 1 Malignancy History – questions 3, 4, 5 and 6 (a, b, & c)

Form 540: Post Baseline Malignancies - all questions, from all forms, from all visits that have been completed up to the date that the malignancy was detected.

Form 560: Malignancy PCAE-SI Pre- or Post- Randomization – Questions 1 thru 15

Final adjudication

Form 530: Baseline /Visit 1 Malignancy History – questions 3, 4, 5 and 6 (a, b, & c)

Form 540: Post Baseline Malignancies - all questions, from all forms, from all visits that were completed.

Form 560: Malignancy PCAE-SI Pre- or Post- Randomization – Questions 1 thru 15

Version 3.0: Appendix B

Version 3.0: Appendix D

Addition of the following Reviewers:

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1. Introduction

Prasugrel hydrochloride (CS-747, LY640315, hereafter referred to as prasugrel) is a new thienopyridine adenosine diphosphate (ADP) receptor antagonist. Prasugrel provides faster onset of action, higher levels of platelet inhibition, and less response variability compared with clopidogrel, the current standard of care for dual antiplatelet therapy in subjects with acute coronary syndromes (ACS), such as unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI). In the Phase 3 study TRITON-TIMI 38 (Wiviott et al. 2006; Wiviott et al. 2007[a]), prasugrel significantly reduced the rate of atherothrombotic events in subjects with ACS undergoing percutaneous coronary intervention (PCI). The present study, H7T-MC-TABY (hereafter referred to as “TRILOGY ACS”), will include subjects who have experienced recent UA and NSTEMI and who will be managed without acute coronary revascularization; that is, who will be medically managed.

In TRITON-TIMI 38, a higher number of prasugrel-treated patients (175/6741, 2.60%) compared to clopidogrel-treated patients (138/6716, 2.05%) experienced an adverse event coded to the “Neoplasms Benign, Malignant, and Unspecified (including Cysts and Polyps)” system organ class (HR=1.26; p=0.043). After excluding non-neoplasms and benign neoplasms, there was a higher incidence of non-benign GI neoplasms in the prasugrel treatment group. The Sponsor concluded that, although a possible causative effect or play of chance could not be excluded, the imbalance most likely resulted from the higher incidence of bleeding in the prasugrel group bringing more events to medical attention (i.e., a detection or ascertainment bias).

During review of the application, the FDA expressed concern that prasugrel may promote tumor growth and requested follow-up information on these patients. Additional data were obtained on 311 of the 313 patients. Follow-up information included tumor type, tumor location, malignancy status (benign, non-benign, or unknown), events prompting evaluation leading to diagnosis (e.g., evaluation of GI bleeding), presence of metastasis, and vital status after database lock. A number of the 311 patients were determined to not have had a neoplasm based on follow-up information from the investigator. Based on the neoplasm event classification discussion in October 2008 between the sponsor and the FDA, there were a total of 174 new, nonbenign neoplasms diagnosed after the start of the study drug (Prasugrel n=94/6741(1.39%), Clopidogrel n=80/6716 (1.19%).

TRITON-TIMI 38 was not designed to ask nor answer questions concerning drug-induced tumor promotion. Although the Sponsor believes that the currently available data do not provide credible evidence that prasugrel promotes the growth of pre-existing, undiagnosed tumors, a direct causative effect cannot be excluded. Therefore, the Sponsor is planning to collect information on the incidence of neoplasms in the TRILOGY-ACS Study. This study has an external oncology working group to provide expert oversight on the data collection and analysis of neoplasm events. Because, like TRITON, TRILOGY ACS is not designed to rigorously answer questions about cancer, and even the most thorough data collection and analysis will have limitations.

2. Role of the DCRI CEC for Cancer Adjudication

To adjudicate the potential cancer events in a uniform and consistent way, a group of external experts, known as the Clinical Endpoint Committee (CEC) for Cancer Adjudication or the CEC-CA (which is separate from the Clinical Endpoint Committee for adjudication of other events in this trial), has been formed. The CEC-CA is blinded to treatment allocation.

The DCRI CEC group is responsible for the conduct of the CEC operations for the TRILOGY ACS study in collaboration with the sponsors, Lilly and Daiichi Sankyo, and the CRO, Quintiles. The DCRI CEC, along with the sponsors, will create, maintain and approve the CEC-CA charter. The DCRI CEC will collaborate with the CRO and sponsors in the development of cancer endpoint eCRF and adjudication pages designed to capture key data required for the efficient and accurate adjudication and final analysis of non-benign neoplasm. For subjects that have either a new malignancy or the recurrence of a previous cancer, the CEC-CA will adjudicate their clinical course at two different time points. These two time points are the time of first detection of the malignancy and at study end (see section 4.4). The items that will be evaluated by the CEC-CA at the initial detection are the following:

- confirmation of malignancy
- date of initial detection of malignancy
- date of histological diagnosis of malignancy
- location of primary malignancy
- stage of malignancy at time of diagnosis and/or general classification (local disease, regional disease, metastatic disease)
- confirmation if malignancy is a recurrence of a cancer that was present prior to randomization
- method(s) by which the malignancy was initially detected

The items that the CEC-CA will evaluate at study conclusion or at the time of death (for patients who die before study conclusion) for patients who have a positively adjudicated new or recurrent malignancy are:

- date of final assessment for neoplasm
- status of disease at final assessment (or at the time of death, when appropriate)

The CEC-CA will confirm the occurrence and the onset date of each suspected cancer based on the preponderance of evidence and clinical judgment of the expert physician reviewers. If there is a discrepancy between the CEC-CA adjudication result and the site-reported data, including date of event onset, the CEC adjudication result will override the site reported data and will be used in the final statistical analysis.

The cause of death adjudication results from the CEC-CA will be separately adjudicated and recorded compared with the cause of death adjudication results from the main CEC (where cardiovascular death is a component of the composite primary endpoint of the study). The CEC-CA will only adjudicate whether deaths were malignancy-related or not malignancy-related and will only evaluate deaths for patients who had a preceding positively adjudicated new or recurrent malignancy. It is expected that there will be disagreement between the main CEC death adjudication results and the CEC-CA death adjudication results for the applicable patients. No attempts will be made to resolve these disagreements for the purposes of the main study efficacy results. The CEC-CA death adjudication results will be utilized only for analyses, presentations, and publications relating to the cancer adjudication activities within this study whereas the main CEC death adjudication results will be utilized for all other analyses, presentations, and publications related to the main study results. In particular, the primary endpoint analyses of the TRILOGY – ACS study will be performed solely using the main CEC adjudication results. The analyses, presentations, and publications relating to the cancer adjudication activities will list and compile the disagreements relating to the death adjudication results between the main CEC and CEC-CA.

The adjudicated results will be electronically entered into the clinical database by the CEC through InForm™ on an ongoing basis. Adjudication reports in InForm™ will be reviewed by the CRO safety group in real time.

3. CEC Committee Organizations

3.1. Selection of CEC Members for Cancer Adjudication

The CEC-CA will consist of physicians with expertise in the diagnosis and treatment of cancers. These physicians will be selected from Duke University, the Duke Clinical Research Institute (DCRI), and/or outside of Duke. No sponsor representatives will serve on the CEC-CA. The CEC-CA physicians provide clinical expertise in the development of the CEC-CA processes, including the development of event criteria, eCRF, CEC-CA adjudication and reporting forms, as well as in the adjudication of suspected events.

All CEC-CA members must agree to the confidentiality agreement for this project, whether signed as individuals or under the DCRI umbrella. All members must also complete a financial disclosure form provided by the sponsors. A CEC-CA member will not review events/cases from their own institution. Membership is for the duration of the TRILOGY ACS study unless the member is deemed by the CEC-CA, Lilly, Daiichi Sankyo, or their designee as being unable to fulfill his/her responsibilities. These responsibilities include, but are not limited to, adherence to the event adjudication timeline and accurate and consistent application of the event criteria.

3.2. Qualifications of the CEC-CA Physician Reviewers

Oncology: CEC-CA physician reviewers will have the following: a current license to practice medicine; current clinical experience in general oncology (with one member with experience in gastrointestinal cancer); expertise in the diagnosis, staging and management of cancers; board certification or board eligibility; and relevant clinical trial experience.

The CEC-CA will also have a member who is a Gastroenterologist that has a current license to practice medicine; current clinical experience experienced in gastrointestinal related cancers; board certification or board eligibility; and relevant clinical trial experience.

Documentation of the required qualifications is maintained at the DCRI in the form of current curriculum vitae for the CEC-CA selected member.

3.3. Clinical Events Classification Personnel

The CEC-CA process involves the following personnel: CEC Director, CEC-CA Chairperson, CEC-CA Coordinator, CEC-CA Physicians, Clinical Data Assistants, and Clerical Support.

3.3.1. CEC Director

The CEC Director oversees the DCRI CEC-CA activities for this study as well as other events and provides physician level support to the CEC-CA Coordinator during the trial. The CEC Director also identifies an appropriate DCRI faculty level physician to serve as the CEC-CA Chairperson for the TRILOGY ACS study.

3.3.2. DCRI CEC-CA Chairperson

The specific responsibilities of the CEC-CA chairperson include:

- Presiding over CEC-CA adjudication conference calls and meetings
- Supervising the activities of the CEC-CA
- Interfacing with the sponsor and CRO regarding the ongoing activities of the CEC-CA

The CEC-CA Chairperson will oversee the cancer adjudication processes but will not participate in the adjudication of suspected cancer cases.

3.3.3. DCRI CEC-CA Coordinator

A coordinator for DCRI CEC-CA will supervise operations of the CEC-CA for TRILOGY ACS. Specific responsibilities will relate only to cancer adjudication and include but are not limited to:

- Collaboration in the development of CEC-CA processes, including the event criteria, and associated documents with the CEC-CA Chairperson, committee members, CRO, and sponsors.
- Collaboration with the CRO in the design of eCRFs, which facilitate the collection of all necessary data required for event adjudication.
- Collaboration with the CRO to ensure that sites have the necessary tools and training to provide the CEC-CA with complete data required for event adjudication.
- Review and facilitate sign-off of the CEC-CA Charter and associated documents.
- Development of efficient systems and work instructions for CEC-CA.
- Training and oversight for the day-to-day work of the CEC-CA team members.
- Organization and facilitation of CEC-CA meetings.
- Management of workflow and assuring timelines are met.
- Facilitation of any additional source document(s) or data collection requested from the committee by posting and closing queries directly in InForm™.
- Review of all endpoint specific source documents and eCRF data to ensure that data required for adjudication is complete.

3.3.4. CEC-CA Physician Reviewers

The CEC-CA Group will include at least five general medical oncology faculty with one member having expertise in GI-related cancers as well as one gastroenterologist. This group will be responsible for:

1. Collectively adjudicating all reported cancer cases in periodic meetings.
2. Participation in discussions related to event criteria and the application of the criteria, CEC-CA conference calls, and meetings.
3. Communication of scheduling conflicts, including extended time away from the office, to the CEC-CA Coordinator and chairperson.

3.3.5. Clinical Data Assistants

The clinical data assistants (CDA) are responsible for the coordination of the chart review process. The CDAs assemble cases for review and track the status of the review process.

3.3.6. Support Staff

The clerical support team performs the daily processing of documents. Responsibilities include copying and distributing files to the CDAs when needed.

3.4. Contract Research Organization (CRO)

The roles and responsibilities in support of the CEC include:

- Collaboration with the DCRI in the design of eCRFs, which facilitate the collection of all necessary data required for cancer adjudication.
- Collaboration with the DCRI in the development of data specifications for programming subject data listings, CEC-CA adjudication forms, and CEC-CA reports (such as data change reports and status reports) that will be available and printable via InForm™.
- Programming and maintaining subject data listings, CEC-CA adjudication forms, and CEC-CA reports that are required for the CEC-CA to manage the CEC-CA effort.
- Collaboration with DCRI to identify and develop specifications for cancer event triggers.
- Programming cancer event triggers (see Section 4.2 for a detailed definition of “event trigger”).
- Running periodic programmatic checks of the clinical trial database to identify cancer endpoints not reported on an endpoint eCRF.
- Collaboration with the CEC-CA to ensure that sites have the necessary tools and training to provide the CEC-CA with complete data required for cancer event adjudication.
- Monitoring and Source verification of all CEC-CA/endpoint critical eCRF variables (See Section 4.3 Collection of Data).
- Clinical Event Validation & Adjudication (CEVA) department of Quintiles will follow up with site to collect Source Documents (including Source Documents requested by CEC-CA)
- CEVA will receive all source documents from sites and provide them to the DCRI
- CEVA will provide the translation for Source Documents submitted by sites
- CEVA will be the primary contact responsible for managing sites to facilitate the resolution of outstanding CEC-CA eCRF and/or source document queries.

3.5. Study Operations Committee

The Study Operations Committee is comprised of members from the Sponsors (Lilly and Daiichi Sankyo), the CRO, and the Academic Research Organization (ARO).

The roles and responsibilities of the Study Operations Committee include:

- Monitoring the progress of the CEC-CA.
- Approving CEC-CA chairperson and members by reviewing CVs.
- Ensuring that any CEC-CA process changes are implemented by the investigators and by the CRO.
- Informing the CEC-CA of the study's progress by communication with the CEC-CA chairperson.

4. Operations

4.1. CEC-CA Meetings

The CEC-CA will have an initial face-to-face training meeting prior to adjudication of the first case. The members of the CEC-CA will have face-to-face meetings to adjudicate events quarterly or when 15 cases have been identified as being complete and ready for review. The scheduling of CEC-CA meetings will be determined by the rate of event accrual and study closure. Once eCRF entry by sites is underway, CEC-CA meetings are projected to occur on a regular basis. For cancer adjudication, all cases will be adjudicated by the CEC-CA committee consisting of at least three faculty members during periodic meetings.

4.2. Identification of Suspected Cancers

The primary method for identification of cancer cases for this study is by investigator-reporting of these events. Investigators will complete cancer-specific endpoint reporting pages for each endpoint event. After initial queries of the eCRF, CEC-CA critical variables will be resolved, designated source documents will be obtained, and data will be cleaned. Once all of these items have been resolved, these investigator-reported cancer events will be adjudicated by the CEC-CA.

The regular CEC for TRILOGY ACS may also identify additional unreported cancer events through the review of source documents submitted for adjudication of cardiovascular endpoint events or if malignancy is selected as the primary cause of a non-cardiovascular death (event trigger). In addition to the investigator-reported endpoint events, potential unreported endpoint events will be identified by a SAS program run by the study statistician. The program will compare preferred terms that are specified by physician reviewers from DCRI, Daiichi Sankyo and Eli Lilly to investigator reported endpoints. The sites will be asked to enter these events into the eCRF. If a site declines

this request than the unreported events will be referenced as CEC-identified suspected cancer events and will be adjudicated by the CEC-CA for review.

4.3. Collection of Data

The cancer endpoint eCRFs are designed to capture the critical data for the event adjudication, including a detailed event narrative. In addition, specific source documents will be required for the cancer adjudication process (see Appendix A). To assist the study sites in identification of necessary source documentation to be sent to the CEC-CA, the eCRF will provide a real-time prompt to the site for the required documents. Sites are instructed to complete the cancer endpoint reporting eCRF pages and submit all required source documents to the CRO as soon as they become aware of the event. Should all the source documents not be submitted with the initial eCRF endpoint report or if additional source documents are needed by the physician reviewers or CEC-CA Coordinator, a query will be posted by the DCRI CEC-CA Coordinator or designee directly into InForm™. The sites will submit the additional information directly to Quintiles CEVA who in turn will send to DCRI CEC-CA. Once the complete and correct data have been received, the query is closed by the DCRI CEC-CA Coordinator or designee. Other than posting the initial CEC-CA queries for incomplete or additional source documents, the DCRI CEC-CA does not have direct contact with sites. Therefore, the CRO is responsible for following up with sites on source document requests, the resolution of eCRF endpoint reporting queries, and working with the sites to obtain translation of any required source documents prior to DCRI CEC-CA submission.

Every effort should be made to provide the CEC-CA with clean eCRF data (see Appendix B for a full list of CEC-CA critical variables) and all required clinical data prior to event adjudication. However, it is possible that eCRF data may be updated or additional clinical data may become available subsequent to the initial event adjudication. Data Change reports will be generated monthly from the database and will be reviewed to identify changes to CEC-CA critical variables for cases already reviewed. The CEC-CA adjudication eCRF and database will subsequently be updated to reflect any changes that are a result of new clinical data and in accordance with the adjudication process described in this charter.

Events with unknown dates will not be adjudicated until after they are query clean and monitored. All needed source documents must be received by the CEC-CA prior to event adjudication

4.4 Cancer Definitions

The following definitions will be utilized by the CEC-CA for purposes of adjudication.

Has a malignancy occurred? The CEC-CA will answer yes to this question if the subject has either evidence of a new malignancy or the first recurrence (during the study period) of a previous cancer.

New Malignancies:

1. New primary cancer in patients with or without pre-existing cancer and/or

2. New metastatic cancer in patients without previous diagnosis of cancer or
3. New metastatic cancer of a clearly distinct histology from any pre-existing cancer.

Recurrence of previous cancer:

1. Evidence of diagnosis of cancer recurrence (histological, imaging or clinical) of a pre-existing cancer, AND
2. History of this pre-existing cancer at time of randomization (i.e., diagnosis of original cancer pre-dates randomization) AND
3. No evidence to indicate based on histological type or clinical picture that this is a different cancer.

Date of Initial Detections: This will be the date of initial detection by a treating physician, when the patient demonstrated either clinical symptoms or diagnostic testing results (for example, imaging, laboratory) with evidence of cancer that allows for a probable clinical diagnosis. Whichever date can be confirmed to occur first will be used.

Date of histological diagnosis: This will be the date that the diagnosis of cancer was documented by histological and/or cytological evidence.

Status of Disease: The following definitions will be used both by, the CEC-CA at the time of the Final Malignancy Adjudication, as well as by the sites during their follow-up visits:

1. No evidence of disease: A patient who after treatment has normal tumor markers and no evidence of disease on physical exam or imaging studies.
2. Stable/Inactive disease: A patient that has evidence of disease, but is not progressing, and has had no new and/or change in treatment since their previous evaluation.
3. Active disease: A patient who has evidence of disease and has either had a new and/or change in treatment since their previous evaluation or could be eligible for a new and/or change in treatment but either refused or did not receive the therapy for another clinical reason (e.g. terminal disease for which alteration in treatment would not be expected to meaningfully prolong life expectancy).
4. Not Applicable: Is used to describe cases for which there is not enough information to indicate a classification.

Stage of malignancy at diagnosis:

1. Stage 0: Carcinoma in situ (early cancer that is present only in the layer of cells in which it began).
2. Stage 1:
3. Stage 2;
4. Stage 3:
5. Stage 4: The cancer has spread to another organ.
6. Staging Incomplete: Is used when the event can not be qualitatively staged as Stage 1-4. In these cases the event will then be classified as:
 - a. Local Disease: Is cancer that is limited to the organ in which it began, without evidence of spread.

- b. Regional Disease: Is cancer that has spread beyond the original (primary) site to nearby lymph nodes or organs and tissues.
 - c. Metastatic Disease: Is cancer that has spread from the primary site to distant organs or distant lymph nodes.
 - d. Not Applicable
 - e. Unknown: Is used to describe cases for which there is not enough information for the reviewer to make an informed decision
- 7. Not Applicable
 - 8. Unknown: Is used to describe cases for which there is not enough information for the reviewer to make an informed decision

Date of final assessment for neoplasm: This will be the date of the final medical information available to the CEC-CA for the assessment of the patient's neoplasm before the close of their participation in TRILOGY. For example, this could be the date of the final study visit, date of death, or date obtained from other source documents such as oncology records, whichever is most clinically relevant.

Cause of death (malignancy-related vs. not malignancy-related): A malignancy-related death will be defined as a death that was directly related to the progression of a given malignancy or due to complications from treatments that were administered specifically for the malignancy (e.g. – chemotherapy, radiation, immunotherapy, surgical resection). Malignancy-related deaths will only be determined when there is sufficient source documentation that describe the patient's clinical condition and treatment before and at the time of death and/or when an autopsy report is available. All other deaths, including those with insufficient source documentation, un-witnessed deaths at home, or sudden deaths without a clear relationship to malignancy progression will be determined to be not malignancy-related.

Additional source documentation will be requested (listed in Appendix A).

4.5. CEC-CA

The CEC-CA will adjudicate cause of death (malignancy-related or not) in all subjects with malignancy at any point in the study, independent of the primary CEC. However, the primary endpoint and all other pre-defined analyses involving attributed death would employ the primary CEC adjudication.

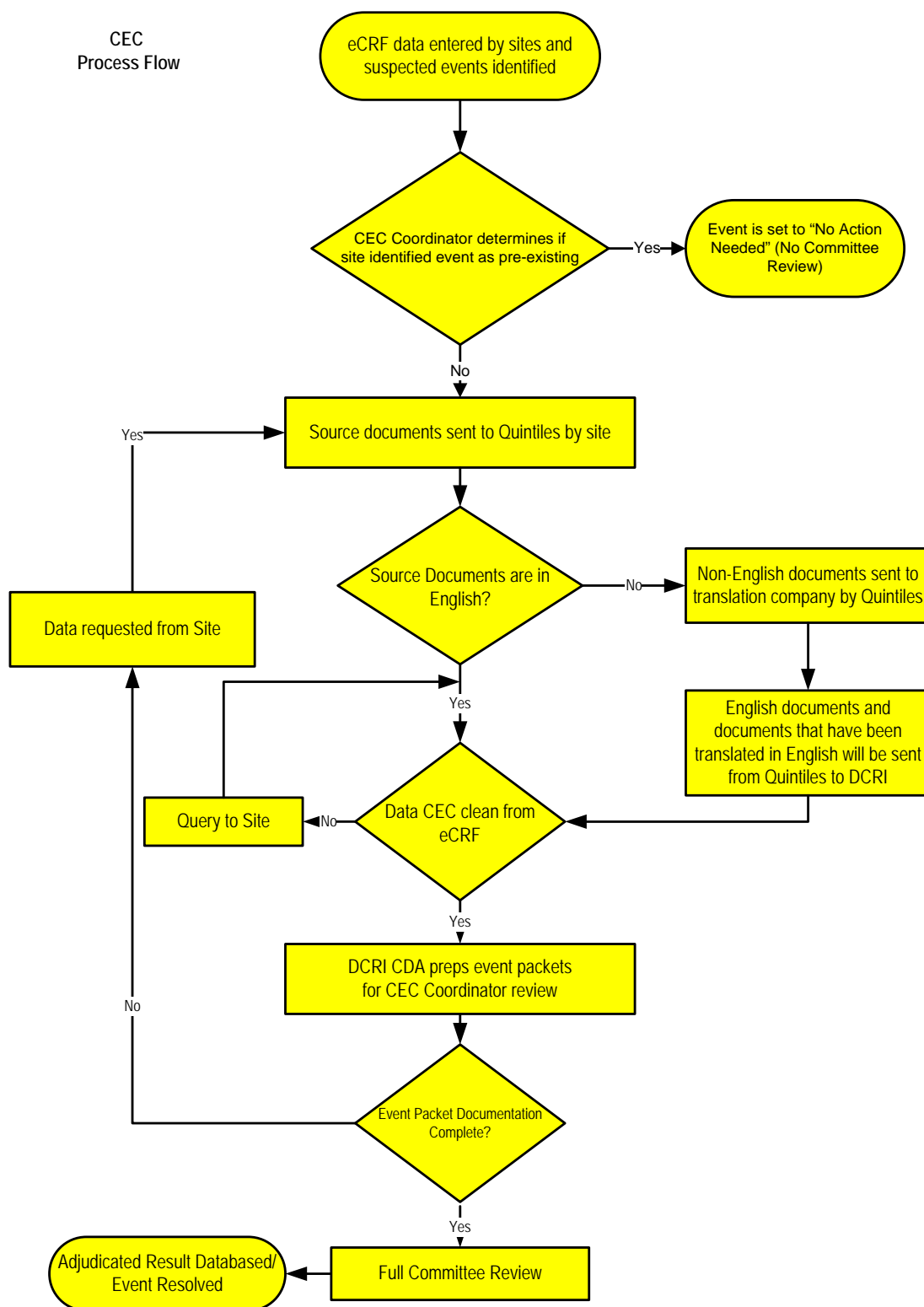
4.6. Quality Control (QC)

The physicians that comprise the CEC-CA will be a consistent, specialized group of reviewers. Due to the fact that all cases will be adjudicated by consensus decisions of this group, additional quality reviews are not considered necessary.

5. Confidentiality

All members must acknowledge in writing that all reports, meeting discussions, and minutes are strictly confidential. Members must also sign a Confidentiality Agreement and Financial Disclosure.

6. CEC-CA Process Flow



7. Documentation

The following guidelines should be followed for retention of CEC-CA documents:

- The original source documents should be archived at the investigative site.
- Meeting minutes from the CEC-CA will be maintained in a CEC-CA archive at DCRI on site and forwarded to the sponsor at the completion of the study. Meeting minutes will consist of the following: attendance roster; list of cases reviewed; documentation of any cases that lead to “Review Conventions”. The “Review Conventions” will be an ongoing list of clarifications on how the study definitions are applied to specific clinical scenarios to ensure consistency in adjudication throughout the life of the study.
- At the end of the study, the CEC-CA forms and supporting documents will be sent to the CRO for archiving. Relevant documents pertaining to events will be collated by subject number and kept in a confidential archive forwarded to the CRO.
- An exact copy of each dossier submitted to the CEC-CA, as well as any data collected in response to CEC-CA requests for additional documentation, will be maintained on file by the CRO.
- Original, final CEC-CA adjudication forms and resolved adjudication form queries will be maintained by the CRO.

Appendix A: Source Documents Needed for Events

Endpoint Type	Source Documents
Cancer	<ul style="list-style-type: none">◆ Reports from pathological evaluation of biopsy specimens◆ Relevant laboratory findings such as cancer marker laboratory reports, and imaging (CT/MRI/PET scan) reports◆ Notes of Oncology/Radiation Oncology Consultation◆ Surgical Consultation report and operative reports◆ Treatment summaries and reports◆ Autopsy reports
Malignancy Related Death	<ul style="list-style-type: none">◆ Clinical notes◆ Autopsy reports

Appendix B

CEC-CA Critical Variable Data - Fields that must be query clean prior to submitted endpoint dossier for adjudication.

Initial Diagnosis

Form 530: Baseline /Visit 1 Malignancy History – questions 3, 4, 5 and 6 (a, b, & c)

Form 540: Post Baseline Malignancies - all questions, from all forms, from all visits that have been completed up to the date that the malignancy was detected.

Form 560: Malignancy PCAE-SI Pre- or Post- Randomization – Questions 1 thru 15

Final adjudication

Form 530: Baseline /Visit 1 Malignancy History – questions 3, 4, 5 and 6 (a, b, & c)

Form 540: Post Baseline Malignancies - all questions, from all forms, from all visits that were completed.

Form 560: Malignancy PCAE-SI Pre- or Post- Randomization – Questions 1 thru 15

Appendix C: List of CEC-CA Personnel

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Appendix D: CEC Committee Members

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Statistical Analysis Plan

last updated: April 8, 2014

Project: TRILOGY ACS: *Risk of New, Non-Benign Neoplasms with Use of Prasugrel (5625-14, TRILO021)*

Primary Investigator: Matthew Roe, M.D., M.H.S.

Co-Investigator(s): N/A

Principal Statistician: Derek Cyr, Ph.D.

Mentor Statistician: Phillip Schulte, Ph.D.

Specific Aims:

- Describe the baseline characteristics, rates of permanent study drug discontinuation, and outcomes (ischemic and bleeding events) for all treated subjects with vs. without a new, non-benign neoplasm event. *Note: Due to the limited number of patients with neoplasm, the individual components of the primary efficacy endpoint are not considered for analysis.*
- Characterize the timing and accrual of new, non-benign neoplasm events for all treated subjects.
- Determine factors (baseline characteristics at the time of randomization) associated with having a new, non-benign neoplasm event among all treated subjects.
- Among treated subjects without a baseline history of malignancy or with curative treatment for a malignancy prior to randomization, examine differences between treatment groups with regards to occurrence and timing of new, non-benign neoplasms, types of neoplasms, locations, stages, and method of detection.

Study Populations:

- Two TRILOGY ACS populations will be used:
 - All subjects treated with study drug (N=9240).
 - Subjects who were treated with study drug and did not have a baseline history of malignancy or had curative treatment prior to randomization (N=9105).
 - *Note: The population considered is specified for each analysis objective.*

Endpoints:

- New, non-benign neoplasm
- Efficacy endpoints:
 - Cardiovascular death, MI, or stroke
 - All-cause death
- Safety endpoints:
 - GUSTO severe, life-threatening or moderate bleeding
 - TIMI major or minor bleeding

Analysis Objectives & Tasks:

Objective 1: Compare the baseline characteristics of treated subjects with vs. without a new, non-benign neoplasm event.

Analysis: Baseline characteristics including demographics, presentation characteristics and medical history will be presented for treated subjects with a new, non-benign neoplasm event vs. those without a new, non-benign neoplasm event. Categorical variables will be presented as counts

(percentages). Continuous variables will be presented as medians (Q1, Q3). Because the comparison groups are defined by a post-baseline event, p-values will not be presented.

- Population considered: All subjects treated with study drug (N=9240).
- See Appendix for proposed Table 1: Baseline Characteristics of Randomized Subjects Treated with Study Drug.
- Note: When presenting a baseline table by a factor not known at baseline (e.g. event status), caution should be taken when drawing conclusions about any difference observed because (1) censoring may imply that we do not have the correct allocation of subjects in the neoplasm vs. no neoplasm groups and (2) there may be differential lengths of follow-up among the subjects in the cohort (e.g. how can we say that a subject who did not have a neoplasm at 6 months (the end of his follow-up) is the same as a subject who did not have a neoplasm at 18 months (the end of his follow-up)?).

Possible conclusions: As no p-values are provided, this table will only describe the patients.

Objective 2: Summarize rates of study drug discontinuation for all treated subjects with vs. without a new, non-benign neoplasm event.

Analysis: A table will be created that describes the primary reason(s) for permanent discontinuation of study drug (e.g., subject had a procedure, adverse event, need for oral anticoagulation, etc...). Descriptive statistics, such as the median time to discontinuation, will also be presented between treated patients with vs. without a new, non-benign neoplasm event. To determine if the frequency of study drug discontinuation differs across groups, the Pearson chi-square test (or Fisher exact test if cell frequencies are not sufficient) will be used. In addition to the table described above, a similar table will be created using only the patients diagnosed with a new, non-benign neoplasm during follow-up that breaks down the frequency of permanent study drug discontinuation before and after diagnosis of a new neoplasm event.

- Population considered: All subjects treated with study drug (N=9240).
- See Appendix for proposed Table 2a: Primary Reason for Study Drug Discontinuation.
- See Appendix for proposed Table 2b: Primary Reason for Study Drug Discontinuation Before and After Diagnosis of a New, Non-Benign Neoplasm Event.

Possible conclusions: For each reason given for discontinuation of study drug, a p-value < 0.05 suggests that the respective frequencies differ across the groups.

Objective 3: Summarize the total number of ischemic and bleeding events for all treated subjects with vs. without a new, non-benign neoplasm event.

Analysis: For descriptive purposes only, a table will be created that presents event counts (percentages) that occur in treated patients with vs. without a new, non-benign neoplasm event. In addition to the above table, for treated patients with a new, non-benign neoplasm event, a second table will be created that presents ischemic and bleeding event counts that occur before and after a new, non-benign neoplasm event. The following efficacy and safety endpoints will be summarized in both tables: cardiovascular death, MI, or stroke, all-cause death, GUSTO severe, life-threatening, or moderate bleeding, and TIMI major or minor bleeding. *Note: Event counts will be tabulated in the subset of patients who did not die of malignancy.*

- Population considered: All subjects treated with study drug (N=9240).
- See Appendix for proposed Table 3a: Total Number of Ischemic and Bleeding Events.

- See Appendix for proposed Table 3b: Total Number of Ischemic and Bleeding Events among Treated Subjects Before and After a New, Non-Benign Neoplasm Event.

Possible conclusions: No p-values will be reported, so this table will only summarize event counts (percentages) in patients with and without a new, non-benign neoplasm event.

Objective 4 Determine factors (baseline characteristics at the time of randomization) associated with having a new, non-benign neoplasm event among all treated subjects.

Analysis: A Cox regression model will be constructed to assess which baseline factors are associated with having a new, non-benign neoplasm event. The initial model will adjust for the following factors: gender, age (continuous), weight (continuous), NSTEMI, history of hyperlipidemia, history of diabetes, current/recent smoking, number of years using tobacco products (continuous), prior MI, prior PCI or CABG, prior PAD, prior heart failure, prior atrial fibrillation, hemoglobin (continuous), creatinine clearance (continuous), PPI use at randomization, and region (3-level: North America vs. Western Europe vs. Other). Using this model, a variable-selection technique will be applied to reduce the model to a set of covariates that are most strongly associated with having a new, non-benign neoplasm. The modeling assumptions of proportional hazards and linearity (for continuous covariates) will be evaluated and any violations will be accounted for. To illustrate which variables are most strongly associated with having a new, non-benign neoplasm event a table will be created that lists each covariate in descending order of chi-square values.

- Population considered: All subjects treated with study drug (N=9240).
- See Appendix for proposed Table 4: Associations of Selected Baseline Characteristics with Occurrence of New, Non-Benign Neoplasm Event.

Possible conclusions: A p-value < 0.05 suggests that the respective covariate is statistically significantly associated with having a new, non-benign neoplasm event.

Objective 5: Among treated subjects without a baseline history of malignancy or with curative treatment for a malignancy prior to randomization, examine differences between treatment groups with regards to occurrence and timing of new, non-benign neoplasms, types of neoplasms, locations, stages, and method of detection.

Analysis: For this analysis, a table will be created that summarizes the occurrence and timing of new, non-benign neoplasms, types of neoplasms, locations, stages, and methods of detection by randomized study treatment (summary totals will also be reported in tables). As was done in analyses provided by the sponsor, the risk of developing a new, non-benign neoplasm will be compared between treatment groups using Cox proportional hazards regression controlling for treatment, clopidogrel status at randomization, and age group. The hazard ratio (95% CI) for prasugrel vs. clopidogrel and two-sided p-value based on a log-rank test stratified by clopidogrel status at randomization and age group will be reported. In summarizing the frequencies of types of neoplasms, locations, stages, and methods of detection, a two-sided p-value based on Fisher's Exact test will be reported. To describe the overall estimated risk of neoplasm for prasugrel and clopidogrel treated patients, cumulative incidence curves will be constructed to illustrate the time from treatment start to the occurrence of a new, non-benign, neoplasm event. To compare treatment groups, the hazard ratio (95% CI) from Cox proportional hazards regression and p-value will be reported. Furthermore, within each treatment arm, the median time (Q1, Q3) to neoplasm diagnosis will be reported.

- Population considered: Subjects who were treated with study drug and did not have a baseline history of malignancy or had curative treatment prior to randomization (N=9105).
- Note: Time to event will be calculated from time of first dose of study drug to date of initial clinical detection.
- See Appendix for proposed Table 5: Subjects with New, Non-Benign Neoplasms - CEC Adjudicated. All Treated Subjects without Baseline History of Malignancy or with Curative Treatment.

Possible conclusions: For each characteristic listed, a p-value < 0.05 suggests that the respective frequencies are statistically significantly different between treatment groups. A hazard ratio p-value < 0.05 suggests that the incidence of new, non-benign neoplasm events is significantly different (direction dependent on if $HR < 1$ or $HR > 1$) between treatment groups.

ADDENDUM: Supplemental Analyses (Included in June 4th, 2014 Statistical Analysis Report):

1. Baseline/Visit 1 Malignancy History.
2. Post Baseline Malignancies.
3. Baseline and Post Baseline Malignancies by Region.

Appendix of Proposed Tables

Table 1.

Baseline Characteristics of Randomized Subjects Treated with Study Drug.

Characteristic	New, Non-Benign Neoplasm (n=170)	No New, Non-Benign Neoplasm (n=9070)
Demographics		
Female Sex (%)		
Age (years)		
Age ≥ 75 (%)		
Weight (kg)		
Weight <60 kg (%)		
Region		
Central/Eastern Europe		
East Asia		
Indian Subcontinent		
Latin America		
Mediterranean Basin		
North America		
Western Europe/Scandinavia		
Rest of World		
Presentation Characteristics		
Hours from presentation until start of study drug		
Killip Class II-IV on presentation (%)		
Disease Classification (%)		
Unstable Angina		
NSTEMI		
Cardiovascular Risk Factors		
Family history of CAD (%)		
Hypertension (%)		
Hyperlipidemia (%)		
Diabetes Mellitus (%)		
Current/recent smoking (%)		
Cardiovascular Disease History		
Prior MI (%)		
Prior PCI (%)		
Prior CABG (%)		
Prior PAD (%)		
Prior Heart Failure (%)		

Table 1.

Baseline Characteristics of Randomized Subjects Treated with Study Drug.

Characteristic	New, Non-Benign Neoplasm (n=170)	No New, Non-Benign Neoplasm (n=9070)
Prior Atrial Fibrillation (%)		
Baseline Risk Assessment		
GRACE Risk Score		
Baseline Laboratory Assessment		
Hemoglobin (g/dL)		
CrCl by Cockcroft-Gault Formula (ml/min)		
Pre-Randomization Treatments		
Clonidine strata (%)		
Stratum 1 - No clonidine		
Stratum 2 - Clonidine started in-hospital ≤ 72 hrs.		
Stratum 3 - Home clonidine		
Angiography Performed (%)		
Concomitant Medications at Randomization		
Aspirin (%)		
Daily Dose <100 mg		
Daily Dose 100-250 mg		
Daily Dose >250 mg		
Beta-Blocker (%)		
ACE-I/ARB (%)		
Statin (%)		
Proton Pump Inhibitor (%)		

Table 2a.

Primary Reason for Study Drug Discontinuation.*

All Treated Subjects.

Disposition				P-value
	Total n (%)	New, Non-Benign Neoplasm n (%)	No New, Non-Benign Neoplasm n (%)	
Number of treated subjects	9240	170	9070	
Total number with permanent study drug discontinuation	2153 (23.3%)	91 (53.5%)	2062 (22.7%)	
Subject had a procedure				
Adverse event				
Hemorrhagic				
Non-hemorrhagic				
Need for oral anticoagulation				
Investigator decision				
Subject decision				
Study drug unblinded				
Entry criteria not met				
Lost to follow-up				

*Note: The population of all treated subjects is considered (N=9240) in this table. % is the percentage of treated subjects.

Table 2b.Primary Reason for Study Drug Discontinuation Before and After a New, Non-Benign Neoplasm Event.^a

Disposition				P-value
	Total n (%)	Before New, Non-Benign Neoplasm n (%)	After New, Non-Benign Neoplasm n (%)	
Total number of treated subjects with a new, non-benign neoplasm event who also permanently discontinued study drug ^b	91	45	44	
Subject had a procedure				
Adverse event				
Hemorrhagic				
Non-hemorrhagic				
Need for oral anticoagulation				
Investigator decision				
Subject decision				
Study drug unblinded				
Entry criteria not met				
Lost to follow-up				

^a Only treated subjects who were diagnosed with a new, non-benign neoplasm event and who also permanently discontinued study drug are considered in this table (N=91). Time on study treatment is defined as the time (in days) from study treatment start to treatment end + 7 days.

^b Two subjects (2.2%) permanently discontinued study drug on the same day as the initial detection of a new, non-benign neoplasm.

Table 3a.

Total Number of Ischemic and Bleeding Events.

Event	Total n (%)	New, Non-Benign Neoplasm n (%)	No New, Non-Benign Neoplasm n (%)
No. of treated subjects	9240	170	9070
Cardiovascular death, MI, or stroke			
All-cause death			
Death from malignancy			
GUSTO severe, life-threatening, or moderate bleeding			
TIMI major or minor bleeding			

Table 3b.

Total Number of Ischemic and Bleeding Events among Treated Subjects Before and After a New, Non-Benign Neoplasm Event.

Event	Total	Before New, Non-Benign Neoplasm Diagnosis	After New, Non-Benign Neoplasm Diagnosis
No. of treated subjects with new, non-benign neoplasm	170	-	-
Cardiovascular death, MI, or stroke			
All-cause death			
Death from malignancy			
GUSTO severe, life-threatening, or moderate bleeding			
TIMI major or minor bleeding			

Table 4.

Associations of Selected Baseline Characteristics with Occurrence of New, Non-Benign Neoplasm Event.

Characteristic	Chi-square	HR (95% CI)	P-value
Demographics			
Female sex			
Age (years)			
Weight (kg)			
Region (North America vs. Western Europe vs. Other)			
Presentation Characteristics			
NSTEMI vs. UA			
Cardiovascular Risk Factors			
Hyperlipidemia			
Diabetes Mellitus			
Current/recent Smoking			
Number of Years using Tobacco Products			
Cardiovascular Disease History			
Prior MI			
Prior PCI or CABG			
Prior PAD			
Prior Heart Failure			
Prior Atrial Fibrillation			
Baseline Risk Assessment			
Hemoglobin (g/dL)			
Creatinine Clearance (ml/min)			
Concomitant Medications at Randomization			
Proton Pump Inhibitor			

Table 5.

Subjects with New, Non-Benign Neoplasms - CEC Adjudicated.

All Treated Subjects Without Baseline History of Malignancy or with Curative Treatment.

Endpoint	Total n (%)	Prasugrel n (%)	Clopidogrel n (%)	HR (95% CI) ^a	P-value ^b
Total number of subjects treated without baseline history of malignancy or with curative treatment	9105	4554	4551		
New, non-benign Neoplasms	160 (1.76%)	82 (1.80%)	78 (1.71%)		
Status of Malignancy					
No evidence of disease					
Active disease					
Stable/inactive disease					
Cannot be determined					
Not Applicable					
Locations					
Blood					
Bone					
Bone Marrow					
Brain					
Breast					
Cervix					
Colorectal					
Esophagus					
Eye					
Gallbladder					
Kidney					
Liver					
Lung/bronchus					
Lymphatics					
Oral Cavity					
Ovary					
Pancreas					

Pharynx
Prostate
Stomach
Urethral
Urinary bladder
Uterus
Other
Unknown Primary
Basal Cell
Squamous Cell
Melanoma
Skin, Other

Stage of Malignancy

Stage 0
Stage I
Stage II
Stage III
Stage IV
Stage Incomplete
Unknown

Method Used for Initial Detection

Routine cancer screening
Symptomatic cancer screening
Evaluation of bleeding event
Evaluation of anemia
Diagnostic procedures done for a
suspected cancer not associated
with a bleeding event or anemia
Diagnostic procedures done for a
reason/symptom not related to a
suspected cancer bleed event or
anemia

Treatment of Malignancy

Radiation

Chemotherapy
Hormonal
Surgical
Immunotherapy
Other treatment

Hospitalized for malignancy for reasons
other than planned treatment

Yes
No

Metastatic during treatment

Yes
No

Abbreviations: CI = confidence interval, HR = hazard ratio, n = number of treated subjects with neoplasm within the sub-category, NE = not evaluated due to insufficient data.

Note 1: For the summary of new, non-benign neoplasms, % is percentage of treated subjects without baseline history of malignancy or with curative treatment.

Note 2: For each new, non-benign neoplasm category (e.g., status of malignancy, location, etc...), % is percentage of treated subjects without baseline history of malignancy or with curative treatment with a malignancy adjudicated.

Note 3: Time to event is calculated from time of first dose of study drug to date of initial clinical detection.

^a HR and two-sided 95% CI derived using Cox proportional hazards model with treatment, clopidogrel status at randomization, and age group as fixed effects. Two-sided p-value based on a log-rank test stratified by clopidogrel status at randomization and age group.

^b Two-sided p-values based on a Fisher's Exact test.